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MANUAL DE SALUD MENTAL

Rodolfo D. Fahrer
Alfredo Ortíz Fragola

La práctica asistencial y docente de muchos años en el Departamento de Salud Mental del Hospital de Clínicas "J. de San Martín" es el origen de este libro. Se trata de un manual para alumnos y jóvenes profesionales sobre los fundamentos de la salud mental, con una concepción integral del hombre y la matriz ambiental en la que está inserto.

MANUAL DE NUTRICIÓN Y DIABETES

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Este libro se ha ideado como una síntesis didáctica de los conocimientos nutricionales que prevalecen actualmente. Se ha procurado aislar en cada capítulo lo más trascendente del tema de manera tal que no se desvirtúe la información en aras de la brevedad.

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Covid-19 en pacientes privados de libertad en una Unidad de Internación Penitenciaria

Noelia Hojberg[1]; Gabriela Signes[1]; Laura Capizzano[1]; Silvia Pulleiro[1]; José L. Francos[1]

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ABSTRACT:

The prison system had to incorporate measures aimed at the prevention, early detection, isolation and treatment of patients with COVID-19. The Penitentiary Center for Infectious Diseases-Unit 21 was set up as a referral site. A descriptive, observational, cross-sectional study was carried out in which the characteristics, treatment and evolution of patients admitted to the Unit for COVID-19, in the context of detention, were described. In the period studied (May 1-October 15, 2020), 427 cases of COVID-19 were registered in the Federal Penitentiary Service, of which 193 were referred to Unit 21. Of these, 191 (98.9%) were of Male gender, with a median age of 51.5 (RI 32.5). 74 patients (38.3%) had mild forms of the disease, 110 (56.9%) were moderate, 7 (3.6%) were severe. 6 patients (3.1%) required the Intensive Care Unit, of which 2 were admitted to the Unit in critical condition and received less than 48 hours of treatment in our center. There were 4 deaths, 2 from respiratory distress, 1 from brain stem stroke, and 1 sudden death. According to severity criteria, the patients received treatment with ivermectin, corticosteroids, antibiotics, antiaggregant and / or antithrombotic prophylaxis. 66.6% had at least one comorbidity and 22.8%, 2 or more. The documented COVID-19 fatality was 2.07% in our center. This is relevant considering the data reported from other prison populations, for example from American prisons where mortality was 5.5 times higher than in the rest of the population.

Key words: COVID-19, pandemic, jails, Argentina.

Introducción

Con el advenimiento de esta nueva enfermedad provocada por el Síndrome Respiratorio Grave Agudo-Corona Virus 2 (SARS-CoV-2) declarada como una pandemia por la Organización Mundial de la Salud (OMS) el 11 de marzo de 2020, el sistema carcelario se vio en la necesidad de adaptar su funcionamiento. Con este fin se dispuso una serie de medidas destinadas a la prevención, detección temprana y derivación de todos los pacientes con resultado detectable de reacción en cadena de la polimerasa con transcriptasa reversa (RT-PCR) para SARS CoV-2 a nuestro centro, la Unidad 21 del Servicio Penitenciario Federal (SPF) en Argentina. (Disposición N° DI-2020-48-APN-SPF#MJ y Disposición N° DI-2020-58-APN-SPF#MJ)[1]

La unidad 21 es el principal Centro Hospitalario dentro de la órbita del SPF para la derivación de pacientes con patologías infectocontagiosas, se encuentra ubicada en el predio del Hospital de Infecciosas Francisco Javier Muñiz (HIFJM) y cuenta con módulos de aislamiento respiratorio, para el diagnóstico y tratamiento de los mismos.

El primer caso de COVID-19 se detectó en Argentina el 03 de marzo de 2020 en un paciente adulto2, en el SPF fue el 24 de abril en el Centro Penitenciario de La Ciudad Autónoma de Buenos Aires (CABA).

En el mes de julio, debido a la dinámica de la pandemia y el aumento de casos, se fue modificando el criterio de ingreso a la Unidad 21, desde el aislamiento de pacientes sin factores de riesgo a aquellos con factores de riesgo o formas moderadas/severas de la enfermedad.

El objetivo del presente trabajo fue describir las características, tratamiento y evolución de los pacientes internados en la Unidad 21 del SPF por COVID-19, en contexto de detención.

Material y métodos

Estudio descriptivo, observacional, transversal de pacientes ingresados a la Unidad 21 del SPF entre el 1 de mayo al 15 de octubre de 2020.

El diagnóstico de COVID-19 se realizó por RT-PCR o con imágenes tomográficas compatibles más Serología para SARS CoV-2 positiva.

Los datos clínicos se obtuvieron de las historias clínicas de la unidad.

Se consideraron comorbilidades y coinfecciones según los diagnósticos consignados en la historia clínica de derivación.

Se consideró obesidad según índice de masa corporal (IMC) mayor a 30.

Los casos se clasificaron de acuerdo a las definiciones de la OMS en leves moderados, graves y críticos3.

Enfermedad Leve: Pacientes sin comorbilidades, sin imágenes patológicas en Radiografía y/o Tomografía computada de tórax y sin clínica de neumonía.

Enfermedad Moderada: Pacientes con alguno de los siguientes: presencia de comorbilidades y/o imágenes patológicas en Radiografía y/o Tomografía computada de tórax compatibles con COVID-19 según el consenso de la Sociedad Norteamericana de Radiología o con signos clínicos de neumonía (fiebre, tos, disnea, taquipnea) pero sin signos de neumonía grave, en particular SpO2 ≥ 90% con aire ambiente.

Enfermedad Grave: Pacientes con signos clínicos de neumonía (fiebre, tos, disnea, taquipnea) más algunos de los siguientes: frecuencia respiratoria > 30 inspiraciones/minuto, dificultad respiratoria grave o SpO2 < 90% con aire ambiente, también se consideró compromiso extenso por imágenes Radiografía y/o Tomografía computada de tórax compatibles con COVID-19 según el consenso de la Sociedad Norteamericana de Radiología4.

Enfermedad crítica: Requerimiento de Unidad de Terapia Intensiva (UTI) o fallecimiento por causa COVID-19.

El tratamiento fue indicado según la gravedad y la evolución del paciente.

A los pacientes leves se les indicó en un principio cuidados generales y sintomáticos. A partir de julio se comenzó a indicar ivermectina a dosis de 12 mg diarios durante 5 días.

Los pacientes que ingresaron con diagnóstico de COVID-19 moderado, recibieron una asociación de ivermectina a dosis fijas de 24 mg diarios durante 5 días, más azitromicina 500 mg, más meprednisona 20 mg, más ácido acetil salicílico 100 mg, además de antibióticoterapia según imágenes radiológicas compatibles con neumonía o signos clínicos o de laboratorio de sobreinfección bacteriana.

Y a los graves se les agregó tratamiento endovenoso con dexametasona 6 mg diarios y la antibioticoterapia se pasó a vía endovenosa.

Los pacientes críticos fueron derivados a las UTI del HIFJM.

Se indicó enoxaparina como tromboprofilaxis, a los pacientes con valores de dímero D mayores a 3000 y a aquellos con alguno de los siguientes factores de riesgo: antecedentes oncológicos, trombosis previas, reposo prolongado o Trombofilia familiar según las Recomendaciones de tromboprofilaxis y tratamiento antitrombótico en pacientes con COVID-19 de la Sociedad Española de Trombosis y Hemostasia5. La dosis utilizada fue de 60 mg/día subcutánea. Esta indicación se implementó luego de presentarse la muerte de causa tromboembólica, accidente cerebrovascular (ACV) de tronco encefálico, y se mantuvo hasta el alta de los pacientes internados.

Resultados

La población penal al día 15 de octubre de 2020 en el SPF era de 11 495, lo cual representa un 94.24% de la capacidad de ocupación. En el período estudiado (entre el 01 de mayo y 15 de octubre de 2020) se registraron 427 casos de COVID-19 en el SPF, de los cuales 193 fueron derivados a la Unidad 21. Todos los casos fueron diagnosticados con RT-PCR positiva, excepto dos pacientes con RT- PCR negativa, a los cuales se realizó diagnóstico por Tomografía compatible y serología positiva para SARS-CoV-2.

De los 193 pacientes que ingresaron a la Unidad 21, 191 (98.9%) eran de género masculino, con una mediana de edad de 51.5 (RI 32.5).

Presentaron formas leves de la enfermedad 74 pacientes (38.3%), moderadas 110 pacientes

(56.9%), graves 7 pacientes (3.6%). Los pacientes que requirieron UTI fueron 6 (3.1%) de los cuales 2 de ellos ingresaron en estado crítico a la unidad y recibieron menos de 48hs de tratamiento en nuestro centro. Se produjeron 4 muertes, de las cuales 2 fueron por distrés respiratorio, 1 causas tromboembólica (ACV de tronco encefálico) y 1 muerte súbita.

El 66.6% presentaron al menos una comorbilidad y tuvieron 2 o más comorbilidades el 22.8%.

La más prevalente fue, como en la población general la HTA (32%). El tabaquismo estuvo presente en 18% de los pacientes y 16% eran diabéticos. El 6% eran obesos y las enfermedades pulmonares crónicas (asma y EPOC) estuvieron presentes en el 18%.

En 152 de 193 pacientes se realizaron controles de RT-PCR previo al alta y 39 pacientes fueron dados de alta protocolar sin RT-PCR control.

Al día 14, negativizaron RT-PCR 38 pacientes (19.6%), a los 21 días 77 pacientes (39.8%) y a los 28 días lo hicieron 27 pacientes (14%).Tardaron más de 29 días en negativizar RT-PCR 10 pacientes (5.1%), la persistencia más prolongada de RT-PCR positiva se constató en un solo paciente que negativizó a los 42 días.

El 92% tuvo acceso a un diagnóstico imagenológico, 58.5% por tomografía de tórax.

La letalidad documentada fue del 2.07% en nuestro centro. En todas las Unidades del SPF, incluyendo la Unidad 21 fue del 3.27%, y si se excluyen los pacientes que ingresaron a nuestro centro, la letalidad asciende al 4.3% en el resto de las unidades del SPF.

Discusión

De acuerdo a lo documentado hasta la fecha, se conoce que 40% de los casos de COVID-19 desarrollan síntomas leves (fiebre, tos, disnea, mialgia o artralgia, odinofagia, fatiga, diarrea y cefalea), 40% presentan síntomas moderados (neumonía), 15% desarrolla manifestaciones clínicas graves (neumonía severa) que requieren soporte de oxígeno, y 5% desarrollan un cuadro clínico crítico presentando una o más de las siguientes complicaciones: insuficiencia respiratoria, síndrome de dificultad respiratoria aguda (SDRA), sepsis y choque séptico, tromboembolismo y alteraciones de la coagulación, y/o falla multiorgánica, incluyendo insuficiencia renal aguda, insuficiencia hepática, insuficiencia cardiaca, shock cardiogénico, miocarditis, accidente cerebrovascular, entre otros. También se han documentado complicaciones atribuidas a los procedimientos invasivos o no invasivos, realizados durante el manejo clínico del caso. Las complicaciones por COVID-19 se presentan principalmente en personas con factores de riesgo: adultos mayores, fumadores y aquellos con comorbilidad subyacente como hipertensión, obesidad, diabetes, enfermedad cardiovascular, enfermedad pulmonar crónica (por ejemplo, la obstructiva crónica y el asma), enfermedad renal crónica, enfermedad hepática crónica, enfermedad cerebrovascular, cáncer e inmunodeficiencia[3].

La mayoría de nuestros pacientes presentaban factores de riesgo como la edad, sexo masculino, múltiples comorbilidades y tabaquismo.

El género masculino predomina en la población carcelaria, lo cual refleja la proporción vista en nuestro centro1;6.

La prevalencia de comorbilidades como HTA y diabetes fueron similares a las estadísticas reportadas en Argentina7;8. Sin embargo se registró un porcentaje mayor de pacientes asmáticos (12%) en comparación con la prevalencia reportada a nivel nacional la cual asciende al 6%9 y un menor porcentaje de EPOC (6%) y Tabaquismo (18%) los cuales ascienden al 14.5% y 22.2% respectivamente10;8.

Las formas moderadas de la enfermedad por COVID-19 fueron más frecuentes debido al criterio de derivación que se modificó en el transcurso de la pandemia, ya que la mayoría de los pacientes con curso leve de la enfermedad realizaban el aislamiento en los respectivos pabellones de las unidades carcelarias destinadas a tal fin. Los pacientes leves ingresaron principalmente entre el mes de mayo y julio. Cabe destacar la poca frecuencia de evolución a formas graves (3.6%) o críticas de la enfermedad (3.1%), así como la baja letalidad (2.07%) comparado con los datos de la población general en Argentina2, a pesar de la alta prevalencia

de factores de riesgo en nuestra población. Esto es relevante teniendo en cuenta los datos reportados de otras poblaciones penales, por ejemplo de las cárceles estadounidenses donde la mortalidad era 5.5 veces más alta que en el resto de la población11. Es dable mencionar que luego de introducir a la terapéutica la profilaxis con enoxaparina no se registraron eventos ni muertes de causa tromboembólica.

Con respecto al tratamiento, aún no hay evidencia de rigor a pesar de los múltiples estudios clínicos que se están llevando a cabo. Sin embargo hay fármacos que merecen ser tenidos en cuenta antes que todo basados en su perfil de seguridad.

Uno de los pilares en el tratamiento incluye el control de los efectos proinflamatorios y consecuente daño tisular desencadenado por este virus. Entre los estudios a destacar se encuentra el ensayo Randomized Evaluation of COVID-19 Therapy (RECOVERY) en el Reino Unido, el cual informó sus hallazgos de 6425 pacientes asignados al azar a 6 mg / d de dexametasona o atención habitual. En general, la dexametasona resultó en una reducción absoluta de la mortalidad del 2.8% (22.9% frente al 25.7% para la atención habitual). El beneficio fue mayor para los pacientes que estaban recibiendo ventilación mecánica invasiva en el momento de la aleatorización con una mortalidad del 29.3% para la dexametasona frente al 41.4% para la atención habitual12. En tal sentido, se tomó en cuenta su introducción terapéutica vía oral basados en la equivalencia a dosis de 20 mg en aquellos casos con enfermedad moderada y principalmente en aquellos con imágenes compatibles con infiltrados en vidrio esmerilado en tomografía de tórax.

Los eventos tromboembólicos registrados llevaron a considerar la profilaxis en los pacientes con factores de riesgo, tomando en consideración las recomendaciones de la Sociedad española de Hematología5, instaurándose la misma a partir del mes de julio. Previo a esto ya se indicaba ácido acetil salicílico a dosis antiagregantes.

Además de sus propiedades antimicrobianas, la azitromicina se usa a veces por sus propiedades inmunomoduladoras, especialmente en pacientes con trastornos pulmonares crónicos. La azitromicina polariza los macrófagos hacia un fenotipo antiinflamatorio M2 e inhibe las vías de señalización proinflamatorias STAT1 y NFκB13;14. En el contexto de los efectos antiinflamatorios, es de particular interés que la azitromicina se use en pacientes que requieran cuidados intensivos por SDRA no relacionado con COVID-19 y se asocie con una reducción significativa de la mortalidad y un tiempo más corto para la extubación15-17.

El tratamiento antimicrobiano con antibióticos de amplio espectro como amoxicilina/ácido clavulanico, ampicilina/sulbactam o ceftriaxona fue indicado de acuerdo a la clínica y radiología, debido a que en el contexto de pandemia el rescate bacteriológico se torna dificultoso. Su instauración fue temprana conociendo las complicaciones por sobreinfección bacteriana en enfermedades virales respiratorias18.

Se decidió iniciar tratamiento con ivermectina cuando comenzaron a mencionarse los primeros datos de estudios en curso19 debido a que es un fármaco ampliamente utilizado para el tratamiento y control de varias enfermedades tropicales. El fármaco tiene un perfil de seguridad excelente, con más de 2500 millones de dosis distribuidas en los últimos 30 años20. La ivermectina inhibe la replicación in vitro de algunos virus ARN monocatenarios positivos, a saber, el virus del dengue (DNV), virus del Zika, virus de la fiebre amarilla, y otros21-27.

Caly y col. informaron recientemente que la ivermectina es un potente inhibidor de la replicación in vitro del SARS-CoV-228. Los estudios farmacocinéticos en voluntarios sanos han sugerido que dosis únicas de hasta 120 mg de ivermectina pueden ser seguras y bien toleradas29.

Ante la escasez de evidencia y la inminente necesidad de proveer atención y tratamiento a una población vulnerable, se optó por un tratamiento en nuestro centro que pudiera modificar el pronóstico, basado en los conceptos de tratamiento compasivo30 y teniendo en cuenta que se trata de una emergencia sanitaria de la cual fuimos aprendiendo sobre la marcha.

Las drogas utilizadas además de ser aprobadas tanto por Food Drug Administration (FDA), como su homólogo en Argentina la

Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT), son relativamente económicas, accesibles y con un amplio rango de seguridad y efectos adversos conocidos y manejados en la práctica clínica. Lo cual sumado a la evidencia de estudios en curso prometedores31-34, justificaron su utilización en nuestra población con resultados para nosotros muy alentadores, sin dejar de destacar que al ser un estudio observacional se requiere de estudios controlados para definir la eficacia clínica.

Contrariamente a lo esperado para esta población en un contexto de vulnerabilidad social y con un alto porcentaje de factores de riesgo clínicos, las formas graves y críticas fueron poco frecuentes y la letalidad fue menor a la registrada en la población general.

Si bien estos datos no pueden atribuirse a alguna de las medidas terapéuticas tomadas, creemos que la atención temprana y los controles estrictos recibidos pudieron ser los motivos que derivaron en dichos resultados.

Puntos clave

Las cárceles a nivel mundial debieron adecuarse para responder a la actual pandemia COVID-19 en una población vulnerable.

Existe poca literatura acerca del manejo y evolución de los pacientes diagnosticados con COVOD-19 encarcelados.

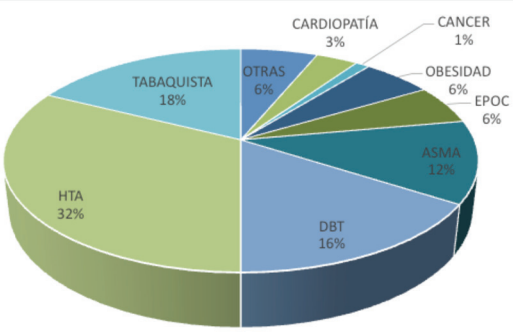
La Unidad 21 fue la respuesta a la demanda de atención en una población vulnerable y con múltiples factores de riesgo en contexto de privación de su libertad ambulatoria.

Nuestro estudio aporta información acerca de cuáles fueron las medidas tomadas para enfrentar la pandemia y los efectos de las mismas en base a la letalidad registrada.

Tabla 1. Características demográficas de los pacientes

CARACTERISTICAS	n	%
Género masculino	191	98.9%
Distribución por grupo de edades		
20-29	32	16.7
30-39	37	19.1
40-49	26	13.5
50-59	32	16.5
60-69	42	21.8
70-79	19	9.8
80 y más	5	2.6

Figura 1. Comorbilidades



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Declaraciones:

Los autores declaran no tener conflictos de interés de ninguna clase, que el trabajo ha sido aprobado por el comité de ética responsable en el lugar de trabajo y no declaran medios de financiación del trabajo realizado.

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RESUMEN

El sistema carcelario debió incorporar medidas destinadas a la prevención, detección temprana, aislamiento y tratamiento de los pacientes con COVID-19. Se dispuso el Centro Penitenciario de Enfermedades Infecciosas-Unidad 21 como sitio de derivación. Se realizó un estudio descriptivo, observacional, transversal donde se describieron las características, tratamiento y evolución de los pacientes internados en dicha Unidad por COVID-19, en contexto de detención. En el período estudiado (01 de mayo-15 de octubre de 2020) se registraron 427 casos de COVID-19 en el Servicio Penitenciario Federal, de los cuales 193 fueron derivados a la Unidad 21. De ellos, 191 (98.9%) fueron de género masculino, con una mediana de edad de 51.5 (RI 32.5). Presentaron formas leves de la enfermedad 74 pacientes (38.3%), moderadas 110 (56.9%), graves 7 (3.6%). Requirieron Unidad de Terapia Intensiva 6 pacientes (3.1%) de los cuales 2

ingresaron en estado crítico a la Unidad y recibieron menos de 48hs de tratamiento en nuestro centro. Se produjeron 4 muertes, 2 por distrés respiratorio, 1 por accidente cerebrovascular de tronco encefálico y 1 muerte súbita. Según criterio de gravedad los pacientes recibieron tratamiento con ivermectina, corticosteroides, antibióticos, antiagregante y/o profilaxis antitrombótica. El 66.6% de los pacientes presentaron al menos una comorbilidad y el 22.8%, 2 o más. La letalidad por COVID-19 documentada fue del 2.07% en nuestro centro. Esto es relevante teniendo en cuenta los datos reportados de otras poblaciones penales, por ejemplo, de las cárceles estadounidenses donde la mortalidad era 5.5 veces más alta que en el resto de la población.

The fallacy of the fat anemic child

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ABSTRACT

Background: studies suggest the presence of iron deficiency among obese children, which would lead to a higher incidence of anemia in this group. Aim: to assess the prevalence of anemia among overweight and obese children from two socioeconomic levels and two different regions in Brazil. Methods: hemoglobin and anthropometric data on 598 overweight and obese children and adolescents were obtained from two services specialized in the care of these children. **Results**: the overall prevalence of anemia was 5.8% and mean hemoglobin level was 13.2 mg/dL, with no statistical difference for the two indicators according to overweight or obesity and age group. However, the mean hemoglobin was higher among boys and, in the service with care provided to a population of lower socioeconomic status, the prevalence of anemia was higher. **Conclusion**: the prevalence of anemia found among overweight and obese children and adolescents was quite low, being higher in the poorest population. For overweight children and adolescents, anemia seems to be more related to socioeconomic status than to the presence of excess weight.

Keywords: Anemia; Overweight; Obesity; Iron; Famine, Occult

Introduction

In 1966, Judisch et al[1] published an article entitled "The fallacy of the fat iron-deficient child", questioning the concept, prevailing at the time, that children with anemia were mostly obese. Currently, it is common the idea that, although it seems paradoxical, obese children, even if they ingest above their energy needs, may have a lack of micronutrients, due to the low quality of food, becoming a risk group for iron deficiency anemia [2, 3]. This possibility was initially suggested by Wenzel et al [4], who verified children with obesity and iron deficiency, observation confirmed by other authors [5-7]. In Brazil, Miraglia et al [8] found a 44% prevalence of anemia among children with a body mass index (BMI) z-score above 2 and, in Bolivia, obesity and anemia coexisted among individuals living on the periphery of metropolitan regions [9].

Iron deficiency anemia is the final stage of iron deficiency, which begins with the depletion of reserves represented by the fall in plasma ferritin [10]. Thus, US data showed, in an article published in 2004, a twice higher risk of iron deficiency among overweight children, using as a criterion the reduction of plasma ferritin [3]. The present study evaluated the hypothesis that, considering that in the literature it is accepted that obesity is a risk factor for iron deficiency [11], the prevalence of iron deficiency anemia among obese children is expected to be high. To test this hypothesis, this prevalence was studied among obese and overweight children, from two socioeconomic levels and two different regions in Brazil.

Methods

Data were obtained from two services in different regions of the country and different customer profiles, between 1998 and 2020: Local 1: private clinic in *Ribeirão Preto*, southeastern region, specialized in nutritional diseases and serving clients with health insurance (n=144); Local 2: public health system patients from specialized obesity clinic at the *Hospital de Clínicas de Porto Alegre* (HCPA) (n = 454). The inclusion criteria were individuals aged between 5 and 18 years, with a BMI z score greater than 1. The exclusion

criteria were impediment to perform anthropometry or absent or incomplete laboratory tests. All patients underwent anthropometric assessment at the first consultation and collected blood samples within 30 days. Anemia patients were considered when hemoglobin was below the cutoff point adjusted for age according to international criteria (10). Anthropometric assessment followed a standardized technique, with overweight being considered when the BMI z score was between 1 and 2 and obesity when it was above 2, according to the World Health Organization curves [12]. Laboratory tests at Local 1 were carried out in one of three certified laboratories that the family could choose, using similar methods and kits, and those from Local 2, in the laboratory of the University Hospital.

The project was approved by the services ethics committees, under the numbers UNAERP 94/2003 and HCPA 07/258.

Results

In the two locations, no differences were observed in terms of distribution by gender (p=0.3900) and by age (p=0.4307). Table 1 shows the prevalence of anemia (total: 5.8%) and hemoglobin averages (total: 13.2 mg/dL), with no statistical difference for the two indicators according to overweight or obesity and age group. However, the mean hemoglobin was higher among boys and, in the service with care provided to a population of lower socioeconomic status, the prevalence of anemia was higher.

Table 1. Prevalence of anemia and hemoglobin values among children and adolescents with overweight and obesity

Group	Prevalence %	p*	Hemoglobin (mg/dL) x ± dp	p**
Boys	4,6		13,4 (1,16)	
Girls	7,1	0,2251	13,0 (0,90)	0,0001
Overweight	5,6		13,2 (0,98)	
Obesity	5,9	1,0000	13,2 (1,08)	0,9685
5 to 9,9 years	4,0		13,1 (0,98)	
10 to 18 years	6,9	0,1536	13,3 (1,09)	0,0693
Place 1	2,1		13,7 (1,05)	
Place 2	7,0	0,0249	13,1 (1,01)	<0,0001
Total	5,8		13,2	

* Fisher exact test
** Mann-Whitney

Discussion

Obesity and anemia are the two most prevalent nutritional diseases in pediatric population. Among school and adolescent age groups, Brazil does not have data on anemia, but local studies from the last 15 years show variable prevalences of 9,3% in Maceió [13]; 22,9% in Niterói [14]; 24,5% in Salvador [15]; 26,9% in Brasília [16]; 16% among school age and 5% among adolescents in Acre [17]; and 19,3% in Campinas [18]. Regarding obesity, the latest national data [19] showed prevalence among adolescents of 27.6% (boys) and 23.4% (girls). Studies carried out since the 1960s showed that obese children were iron deficient and, therefore, would have a higher risk of developing iron deficiency anemia. However, later data of Peru[20], México[21] and India[22], who specifically focused on hemoglobin measurement, did not demonstrate high anemia prevalence among overweight children. According to Sal et al [11], the mechanisms involved in iron deficiency among obese people could be several: poor quality food, high demand for increased blood volume, reduction in myoglobin due to physical inactivity and genetic predisposition. However, the most commonly used marker, ferritin, is influenced by the inflammatory state and may be altered even with adequate iron stores [23]; it is known that obesity is also accompanied by a chronic inflammatory process [24]. Hepcidin, the main controller of iron absorption, is one of the adipokines produced by adipose tissue and has an increased expression in obese people and, supposedly, could contribute to deficiency, as it would decrease the absorption of iron by enterocytes and the export of iron by macrophages and hepatocytes, increasing its sequestration in the spleen and [11, 25]. Thus, ferritin does not seem to be an adequate marker for assessing the nutritional iron status in obese children and, perhaps, there is, probably, no greater risk of iron deficiency anemia directly associated with

childhood obesity. The data of the present study corroborate this hypothesis, since the prevalence of anemia found was extremely low, in two different regions of the country and with different social strata. In the service that treats patients of lower socioeconomic status, the prevalence, although low, was slightly higher, showing that, possibly, the economic factor leading to low nutritional quality food and low in iron of adequate bioavailability [26], is the determinant of the risk of iron deficiency anemia, and not obesity. Further studies are needed to verify whether the alleged iron deficiency associated with obesity is real or just a laboratory artifact. The use of other markers such as hepcidin, hemojuvelin, zinc-protoporphyrin and soluble transferrin receptors, associated with the simultaneous assessment of iron and hemoglobin deficiency markers, could help to clarify this issue.

Declarations

The authors declare that they have no conflicts of interest, that the work has been approved by the ethics committee responsible in the workplace, and do not declare means of financing of the work carried out. Availability of data and materials: available upon request

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RESUMEN

Fundamento: los estudios sugieren la presencia de deficiencia de hierro en niños obesos, lo que conduciría a una mayor incidencia de anemia en este grupo. Objetivo: evaluar la prevalencia de anemia entre niños con sobrepeso y obesidad de dos niveles socioeconómicos y dos regiones diferentes en Brasil. Métodos: se obtuvieron datos de hemoglobina y antropometría de 598 niños y adolescentes con sobrepeso y obesidad de dos servicios especializados en la atención de estos niños. Resultados: la prevalencia global de anemia fue del 5,8% y el nivel medio de hemoglobina fue de 13,2 mg / dL, sin diferencia estadística para los dos indicadores según sobrepeso u obesidad y grupo de edad. Sin embargo, la hemoglobina media fue mayor entre los varones y, en el servicio con atención prestada a una población de menor nivel socioeconómico, la prevalencia de anemia fue mayor. Conclusión: la prevalencia de anemia encontrada en niños y adolescentes con sobrepeso y obesidad fue bastante baja, siendo mayor en la población más pobre. Para los niños y adolescentes con sobrepeso, la anemia parece estar más relacionada con el nivel socioeconómico que con la presencia de exceso de peso.

Ayurveda Treatment (Virechana and Basti) and Changes of Intestinal Microbiota at Phyla and Species Level

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ABSTRACT

Introduction: Ayurvedic therapies and medical practices have been elaborated for some patients in Japan. The characteristic of Ayurvedic treatment is a detoxication with a large amount of oil treatment by body surface oil massage and purgation therapy with ghee or specially arranged herbal oil. Changes of intestinal microbiota during these treatments have not been well studied. **Method:** Participants were recruited from Hatai Ayurveda Clinic in Tokyo. *Virechana therapy,* a purification therapy, or *Basti* therapy (decoction and oil enema) was carried out on 13 patients with various manifestations. All participants provided lifestyle, dietary habits, past, and present illness by the questionnaire, and precise condition was recorded during admission to the end of camp. Fecal samples were taken at the entry, during treatment, at the discharge, and three weeks later for analyzing intestinal microbiota by seqyebcubg 16srRNA gene. **Results**: Body weight decreased by about 5% by *Virechana* therapy, while it did not occur by *Basti*, but body fat increased 4% (2.2 kg) on average in both groups. Various clinical manifestations of participants became improved, especially on a skin rash and atopic change.
The depressed patient also revived with a will of living. They are mostly vegetarians and had more *Bacteroides* (48.09±7.51%), *Firmicutes* (38.27±10.82%), and *Actinobacteria* (3.30± 3.58%) than omnivores who had more *Proteobacteria* (10.73±4.75%)*, Fusobacteria* (2.40±6.25%) and *Cyanobacteria* (0.09± 0.24%). When the groups were divided by oil consumption, ghee users showed higher *Fusobacterium* and less *Firmicutes* and *Actinobacteria. Virechana therapy* caused remarkable microbiota changes after the pretreatment, such as the decrease of *Firmicutes* and increase of *Proteobacteria*. At the genus-species level, the increase of *Enterobacteriaceae* and loss of *Akkermansia municiphila* were noteworthy. *Niruha Basti* and *Matra Basti* decreased *Firmicutes* and increased *Proteobacteria (p=0.096). Fusobacterium* also increased. After the discharge, *Proteobateria* remained high, but *Firmicutes* returned to 30% on average, ranging from 25% to 50%. Three weeks later, the variety increased by *Fusobacterium*, *Verrucomicrobia*, *Tenericutes,* and *Lentisphaerae*. The variety of species also increased three weeks later. **Conclusion:** Various complaints of the participants improved by the Ayurvedic treatment with a large amount of oil treatment by body surface oil massage and purgation therapy. It caused changes in intestinal microbiota, and bacterial metabolites may affect skin lesions and mental health like depressive feeling.
Keywords: Ayurveda; *Virechana, Niruha Basti*, *Matra Basti,* Intestinal Microbiota, *Bacteroides*, *Firmicutes*, *Actinobacteria, Fusobacterium*, *Verrucomicrobia*, *Tenericutes*, *Lentisphaerae,* Purgative, Case study

Introduction

Ayurvedic therapies and medical practices have been elaborated for some patients in Japan.

Ayurveda means the science of life in Sanskrit, emphasizes the adoption of many healing therapies, which can purify and rejuvenate the body, mind, and soul[1-4]. The medicinal form of science is not just a healing system but also an art of appropriate, healthy, and disease-free living[5-7].

Ayurvedic medicine's central concept is the theory that health exists when there is a balance between the three fundamental bodily bio-elements, called *Dosha,* which is composed of *Vata*, *Pitta*, and *Kapha*. *Doshas* are the forces that create the physical body. They determine conditions of growth, aging, health, and disease. Typically, one or two of the three *Doshas* predominates and picks a constitution or mind-body type. By understanding individual habits, emotional responses, and body type, practitioners can adapt their practice accordingly.

A traditional Ayurvedic detoxification program referred to as *Panchakarma* (consisting of five varieties of purificatory therapy) aims to help the body re-establish a healthy metabolic system and immunity[8].

The characteristic of Ayurvedic treatment is detoxification with a large amount of oil treatment by body surface oil massage and purgation therapy (or eliminating therapy) with ghee or specially arranged herbal oil[9]. *Virechana* therapy is an effective Ayurvedic treatment that can cure many health problems naturally. The *Virechana* therapy detox program, which may take seven to14 days, is reported safe from any side effects.

Ayurveda treatments focused on alleviating any excesses *Dosha* (illness) via powerful herbs and/or through the improvement of general lifestyle practices such as *Dinacharya* (daily Ayurvedic rituals practiced regularly, help to support a life of optimal wellness through routine), Pranayama (the regulation of the breath through certain techniques and exercises) and Meditation[3].

Panchakarma therapy encompasses five treatments that can prevent and heal a number of illnesses. *Virechana* therapy is defined as the medicated purgation therapy, which cleanses the excess Pitta, leading to purifying blood by clearing the toxins from the body[10]. The treatment concentrates on the lipophilic toxins that are accumulated in the liver and gall bladder. The gastro-intestinal tract is also cleansed by *Virechana* therapy. *Virechana,* a purification therapy, causes severe diarrhea, but the effects on intestinal microbiota have not been well studied yet. In this study clinical products and changes of intestinal microbiota for 11 days *of Virechana therapy* and 5 or 6 days change by Basti Therapy (alteration of decoction and oil enema) are reported.

2. Subjects and Methods

2.1 Subjects

Participants in the current Ayurveda therapy camp were recruited from patients who had been treated in the Hatai Clinic in Tokyo. They were nine females and four males, with various complaints (Table 1). They are requested to fulfill the questionnaire that was used in the GENKI study[11,12]. It focuses on dietary habits, health status, current illness, family condition, and food preference. Food intake can be calculated from a semi-quantified food frequency questionnaire. Body composition, such as water, muscle, and fat%, was measured during the Tanita Impedance Equipment[13].

Two doctors and the several staffs were accompanied to support this program. Dr. Shiho Oikawa in Panchakarma, who was the registered Ayurveda doctor, graduated from Gujarat Ayurveda University India.

The Ethical Committee approved the study design of the Life Science Promoting Association (No. 2018-3).

2.2 Treatment

Three treatment methods were applied to the participants according to their condition[2-4].

Four patients received a full course of *Virechana* therapy for 11 days, and two received *Sastikashali pinda sweda* (milk porridge Sudation therapy), and one received daily oil. Basti and remedy were done for 11 days. Other six people received *Swedana Basti* therapy, oil massage, and treatment for 5 or 6 days. Milk porridge sudation therapy is meant to improve general strength, including muscle tone, flexibility of the joints movements, and motor impairment syndrome[14].

Two doctors were participated in the program as controls without receiving Ayurvedic therapy.

In *Virechana* therapy, patients drank ghee for four days subsequently ~~and~~ whole body oil massage for three days as the pretreatment, then drank 50ml castor oil on the 9^{th} day. It induces multiple purgations on the day, so the diet needed to change to thin rice porridge and drank two litter raisins juice on the same day to avoid dehydration. After the purgation completed from the next day onwards, they are recommended to take a soft meal avoiding wheat and bread easy to digest.

Table 1, Outline of participants in the Ayurveda treatment camp at Kawaguchi Lake

id	age	time2	Present illness	Drugs	profession	Dietary habit	Staple food
1	42	F	Atopy, Abortion, stomatitis, fever		Ayurveda therapist	Vegetalian	Genmai+barley
2	54	F	Rheumatoid arthritis, insomnia,	Immunosuppressan	Ayurveda therapist	Vegetalian	White rice+barley
3	63	M	Atopy, systemic allergic eruption, Vulvectomy	Anticoaggulant	Retired banker	Balanced flexitarian	Germ rice
4	38	F	Prurritus, delayed type food allergy		Unemployed	Omnivor (like fatty meat)	White rice
5	67	M	Hypertension, Angina, Cerebral infarction, Coronary a. bypass ope. 10 days before	Antihypertension, anticoaggulant	Tax counsellor	Vegetable main, beer	Genmai
6	67	F	Peptic ulcer, stress	none	wife	Omnivor (fish, meat 2-3/W)	White rice/genmai
7	53	F	Hypercholesterolemia, Hypertension	none	Public health nurse	Vegetalian	White rice/genmai
8	56	F	Cervical dyaplasia, Hypercholesterolemia, gallic stone	none	wife	Vegetalian, low salt	White rice+barley
9	49	F	Insomnia, anemia, fatigue, Headache	none	Care worker	Omnivor (pork, fish 1-2/W)	White rice+barley
10	40	F	Asthma, post breast ca, Depressi	none	house wife	Vegetable main, sea weed, fish	White rice
11	53	F	Diabetes, subarachnoid bleeding	none	Yaga studio owner	Vegetable main, seweed, fish	Germ rice/genmai
12	40	F	Deppression	Antideppressant	house wife	Vegetalian	White rice
13	41	M	healthy, fatigue, loose stool	none	Employee	Vegetalian (Chikin, fish 3-4/W)	White rice+barley
14	42	F	healthy control	none	Ayurveda doctor	Omnivor	Partially polished rice
15	46	M	healthy control	none	Medical doctore integrative medicine	Omnivor (chikin, fish 3-4W)	White rice

The small piece of feces was collected four times in the sample tubes at the time of admission, after castor oil drinking, just before discharge (11th day), and then after three weeks at home. The treatment schedule is shown below. (Fig. 1)

Virechana therapy (upper figure): Day 1. *Swedana*: Sweat subjects' whole body in a steam box to improve metabolism and dry their body. Day 2-5 *Snephapana* (internal oleation): After excretion in the morning, face washing and brushing, take 30ml of ghee warmed to human skin temperature at 5:30 am. Then eat nothing until to be hungry. If feel hungry around noon, so eat about half of the usual meal. They have consumed oil inside the body to soften the damaged *Dosha*. On days 2-5, repeat the same procedure as the previous day with a daily increase of ghee from 60 ml to 120 ml. Day 6-8 Abhyanga and *Swedana*: Perform oil massage on the whole body, including the head and sweat from the entire body in the steam box. Infiltrate oil quality from the body surface. On Day 9 purgation was done: Drink laxatives prescribed at 9:30 am (no breakfast). To excrete *Doshas* collected in the digestive tract. Till the end of purgation, the patient drank two litter raisins juice little by little. Thin rice gruel could be taken at night; Day

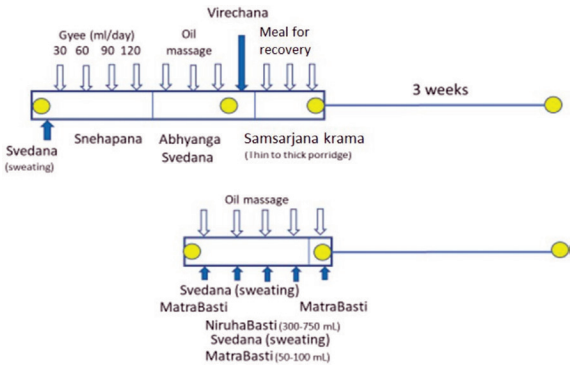

Fig.1 *Panchakarma* in Kawaguchi Camp:

10, 11 *Samsarjana* Krama: Half rice porridge, 70 % rice porridge, and gradually return to the normal diet. After that, patients returned to a normal diet by 5 to 7 days.

Basti therapy (lower figure): Day 1: *Matra Basti*: After a whole body oil massage, including the head, steam sweating was performed, and then 50 to 100 ml of medicated oil was administered from the anus. Keep it until the next day of excretion. On Day 2 to 5: *Niruha Basti* and *Matra Basti*: *Niruha Basti* is performed in the morning empty stomach. After massage and sweating as in the previous day, a 300-750 ml decoction-based drug was administered from the anus. Excretion desire occurs in 5 to 20 minutes and evacuates the bowel contents to the toilet. After Lunch can be taken after excretion. *Matra Basti* is performed in the afternoon to apply oil massage to the abdomen, waist, thighs, and Swedana with a hot towel or steam, and administer 50 to 100 ml of medicinal oil from the anus, which was done after Lunch.

Day 6. (Last day) *Matra Basti*: After a light breakfast, whole body oil massage, steam sweat was performed, and 50 to 100 ml of medicinal oil was administered from the anus. Discharge in the afternoon when bowel movement was settled.

The amount of ghee to drink, the number of days, the combination of herbal medicines taken, the menu of meals, etc. was changed depending on the patient's physical condition and physical strength. The drugs used for the purgation therapy vitiate the Doshas and bring them into the abdomen. While performing the *Virechana therapy*, the vitiated Doshas are eliminated through the rectum.

We have arranged in Japan to split the decoction enteral in the morning and the oil enteral in the afternoon and do both types of Basti on the same day as we did on the second to fourth day. In India, only a kind of enteral is done per day.

2.3 Dietary therapy

The menu of meals was performed in Japanese style food by the Ayurveda dietitian. During the procedure, the patient is subjected to Oleation first, then Fomentation, followed by Purgative and *Samsarjana Karma* (post-operative therapy). The internal Oleation is followed for three to seven days. After that, a medicated steam bath is performed for three days. A light and warm diet is prescribed for the patient a day before starting *Virechana therapy*. However, certain factors like body and mind constitution, age of the person, a mental condition should be considered while opting for *Virechana* therapy *karma*.

Main meals: Rice with cereals (500 g of rice), clear soup (Leek onion, winter melon, ragged kelp, rock salt, soy sauce), Sauce of *Tsurumurasaki* (vine, rock salt, black pepper, unroasted sesame oil), Purple radish with kalonji (purple radish, rock salt, kalonji, Taihaku sesame oil), *Tempura* of lotus root and carrot (lotus root, carrot, rock salt, millet, soy sauce, sesame, unroasted sesame oil), Cumin rice (rice, barley cumin, ginger, ghee), Eggplant and beans curry (onion, cherry tomato, eggplant, beans, unroasted sesame oil, cumin, mustard seed, turmeric, rock salt), Bean curry with winter melon (winter melon, mung bean, ginger, ghee, cumin, turmeric), Okra spice *sauté* (okra, turmeric, coriander seeds, rock salt, unroasted sesame oil), Boiled dried figs with cinnamon (dried figs, cinnamon), Buttermilk (yogurt, rock salt, cumin,ginger, mustard seed, fenugreek, turmeric, ghee) Milk tea with spices (cinnamon, cardamom, clove, tea, milk, cane sugar), Ginger rice (rice, barley, ginger, kelp, rock salt, Shiso leaves, sesame), Corn soup (corn, onion, ghee, rock salt), sautéed radish with sauce (daikon, sesame oil, *kuzu*, Mitsuba leaf, ginger), soak spinach and ginseng (spinach, ginseng, ginger, kelp stock, rock salt, roasted sesame oil, sesame), Punch holon saute of yam (yam, mustard seed, cumin, fennel, karonji, fenugreek, were served during the camp (Fig.2). Black pepper, cumin, brown mustard, coriander, turmeric, garam masala, cinnamon, cardamom, clove, kalonji, ajowan were used for spice[14].

Various kinds of oils, such as ghee, olive oil, white sesame oil, roasted sesame oil, perilla oil, and coconut oil, were frequently used. Rice porridge and mung beans are a digestive meal that helps to recover weak internal organs.

Daily energy intake was adjusted between 1200-1500 kcal (about 30 kcal/kg body weight) depending on the patients' body weight.

Fig. 2. Vegetarian meals during Ayurveda therapy. Each row from upper to lower shows morning, Lunch, and supper in 3 days, and the mid two photos show afternoon teatime snacks (*Shiratama Shiruko* and Jelly).

2.4. DNA extraction from fecal samples

DNA extraction and 16S rRNA was performed as previously described (Vet Microbiol. 2020 Uchiyama). Briefly, the genomic DNA was extracted from the samples using Chemagic DNA Stool 200 Kit (PerkinElmer, Waltham, MA, USA).The V3–V4 regions of the 16S rRNA gene were amplified by PCR and subjected to pair-end sequencing using Illumina MiSeq. The sequence data were processed using Quantitative Insights into Microbial Ecology 2 (QIIME 2) v2019.4.0 (Bolyen et al., 2019). The DADA2 software package v2019.4.0 incorporated in QIIME 2 was used to correct the amplicon sequence errors and construct an amplicon sequence variant (ASV) table. The Greengenes 99% reference database v13.8 was used for the taxonomic classification of each ASV. Microbial taxonomy was assigned using a Naïve Bayes classifier trained on the SILVA 138 database. The sequence data were processed using Quantitative Insights into Microbial Ecology 2 (QIIME 2) v2019.4.0 (Bolyen et al., 2019). The DADA2 software package v2019.4.0 incorporated in QIIME 2 was used to correct the amplicon sequence errors and to construct an amplicon sequence variant (ASV) table.

More details are described in the previous paper[15-18].

The fecal microbiota of 15 subjects was analyzed using the 16S rRNA amplicon sequencing method. A total of 2,032,860 nonchimeric reads (39,860.0±7,307.8 nonchimeric reads/sample; mean±SD) were used in this study. To rarefy the data, we used 24,000 reads from each sample.

2.5 Statistics

Microbial taxonomy was assigned using a Naïve Bayes classifier trained on the SILVA 132 99 % database. First, changes of microbiota were screened at the phylum level. The more detailed analysis was done at the genus-species level if each microbiota occupied more than 1% of the composition. The statistical analysis was performed using statistical software IBM-SPSS ver 24[19] unless otherwise stated. In all statistical analyses, significance was set at $P<0.05$ unless otherwise stated. A paired t-test was used to detect significant changes, and Spearman's correlation analysis and chief component analysis were done to see interrelation of microbiota for proliferation and inhibition. ASV number and Shannon's index were calculated by R software[20].

3 Results

3.1. Anthropometric data

All patients who participated in the Ayurveda therapy camp showed improvement in both clinical and mental condition. (Table 1) The accompanying doctors checked the state of the patients. Especially diarrhea and dehydration were carefully watched. Meditation, yoga, and health lecture were done in between the therapy.

Bodyweight decreased 1.7 to 5.8 kg (3.7±1.8kg) or 3.2 to 9 % (6.4±2.6%) by *Virechana* therapy ($p=0.026$), but there was no significant decrease in other methods. (Table 2). On the contrary, body fat percentage increased significantly in both *Virechana* and *Basti* groups.

Clinical manifestations of participants became better (Fig. 3). It was effective in skin rashes by atopic change. The depressed patient had the will to live.

3.2 Intestinal microbiota at the admission of the camp

At the admission, the most frequent bacteria phylum was *Bacteroides* (46.61±8.90%),

Table 2. Anthropometric change during Ayurveda treatment. The clinical findings decided on the outcome.

id	Treatment	Necessary calorie*	Height	Weight pre	Weight post	Difference kg	Difference %	BMI pre	BMI post	Fat% pre	Fat% post	Difference %	Outcome
1	Virachana	1594	166	49.8	47	-2.8	-5.6	18.1	17.1	20.7	25.1	4.4	better
2	Virachana	1699	158	53.1	51.4	-1.7	-3.2	21.3	20.6	34.4	33.6	-0.8	improved
3	Virachana	1738	166	54.3	50	-4.3	-7.9	19.9	18.4	10.3	16.3	6.0	improved
4	Virachana	2054	167	64.2	58.4	-5.8	-9.0	23	20.9	17.3	23.7	6.4	improved
5	Milk porradge sedation	2371	173	74.1	72.2	-1.9	-2.6	24.8	24.1	27.9	28.4	0.5	improved
6	Milk porradge sedation	1581	155	49.4	48.9	-0.5	-1.0	20.6	20.4	32.4	33.1	0.7	better
7	Basti	1843	162	57.6	57.4	-0.2	-0.3	21.9	21.9	21.8	31.3	9.5	better
8	Basti	1517	152	47.4	47.1	-0.3	-0.6	20.5	20.5	20.4	25.7	5.3	better
9	Basti	1645	171	51.4	51.1	-0.3	-0.6	17.6	17.6	17.5	24.1	6.6	better
10	Basti	2182	154	68.2	67.3	-0.9	-1.3	25.1	17	17.6	23	5.4	better
11	Basti	1606	163	50.2	49.6	-0.6	-1.2	18.9	18.9	18.4	22.2	3.8	better
12	Basti	1299	165	40.6	42	1.4	3.4	17	25.1	23.7	33.8	10.1	calm
13	Basti	1846	173	57.7	57.6	-0.1	-0.2	19.3	19.3	19.2	14.6	-4.6	living will
14	cont	2368	164	74	72	-2	-2.7	27.5	26.7	na	na		
15	cont	2336	167	73	73	0	0.0	26.1	26.1	na	na		
	*calcurated from "body weight (kg) * 0.4 * 80 "												

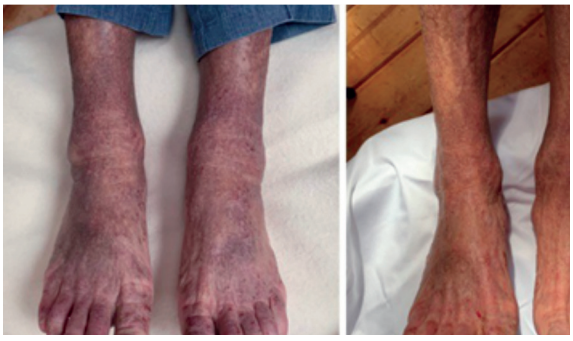

Fig. 3. Improvement of skin rashes by Virchana. Itchy eruptions became flat and not itchy. Left Pro and Right Post.

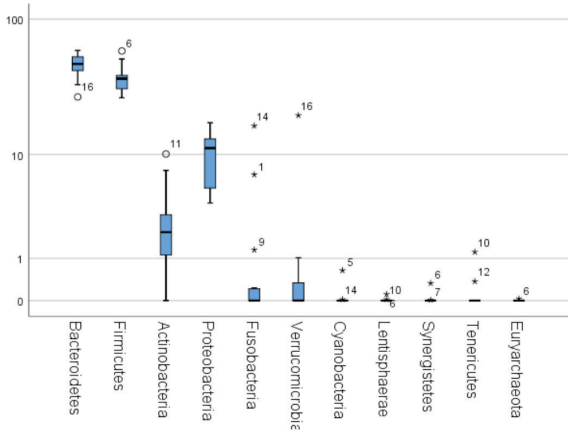

Fig. 4. Frequency of intestinal microbiota profile at the admission

*Firmicutes (*37.5±9.06%), *Actinobacteria* (2.87±3.02%), *Proteobacteria (*9.63±4.38%),

Cyanobacteria (0.04±0.16%), *Fusobacteria* (1.68±4.49%), *Lentisphaerae (*0.01±0.03%), and *Synergistetes* (0.02±0.09%). Another phylum was not detected above 0.1%. (Fig. 2).

Everybody possessed *Firmicutes, Bacteroidetes, Actinobacteria*, and *Proteobacteria*, but others showed variation; *Fusobacteria* 33.3%, *Verrucomicrobia* 46.7%. *Cyanobacteria* 6.7%, *Lentisphaerae,* and *Synergistetes* 13.3% each, *Euryarchaeota* 6.7%, and *Tenericutes* 13.3%. At the discharge, *Tenericutes* increased to 40%, but other phyla returned to the profile at the admission.

Microbiota profile showed different dietary habits pattern, although there was no statistical significance (Table 3a-c). Vegetarians had more *Bacteroides*, *Firmicutes,* and *Actinobacteria* than omnivores, who had more *Proteobacteria, Fusobacteria,* and *Cyanobacteria*.

Kind of staple foods was divided into polished white rice (5), white rice and barley (4), white rice and brown rice (3), and genmai (brown rice) (3). Genmai eaters showed higher Firmicutes and less *Actinobacteria* and *Proteiobacteria*, but "white rice+barley" group also showed the similar trend. Significant difference among groups was not present.

When the groups were divided by oil consumption, ghee users showed higher *Fusobacterium* and less *Firmicutes* and *Actinobacteria* (Table 3c).

Table 3a. Intestinal microbiota by dietary habits at baseline

	vegetalian n=8			omnivor n=7			Total n=15		
	mean		sd	mean		sd	mean		sd
Bacteroidetes	48.09	±	7.51	44.92	±	10.61	46.61	±	8.90
Firmicutes	38.59	±	10.82	36.27	±	7.19	37.51	±	9.06
Actinobacteria	3.30	±	3.58	2.39	±	2.40	2.87	±	3.02
Proteobacteria	8.67	±	4.09	10.73	±	4.75	9.63	±	4.38
Cyanobacteria	0.00	±	0.00	0.09	±	0.24	0.04	±	0.16
Fusobacteria	1.05	±	2.40	2.40	±	6.25	1.68	±	4.49
Lentisphaerae	0.01	±	0.04	0.00	±	0.01	0.01	±	0.03
Synergistetes	0.04	±	0.12	0.00	±	0.00	0.02	±	0.09

Table 3b. Intestinal microbiota by rice intake

	rice											
Baseline	white n=5			white/barley n-4			white/genmai n=3			genmai n=3		
	mean		sd	mean		sd	mean		sd	mean		sd
Bacteroidetes	48.75	±	12.66	43.45	±	4.69	48.53	±	4.05	45.32	±	12.02
Firmicutes	32.99	±	4.84	42.38	±	8.59	33.08	±	5.93	42.98	±	14.47
Actinobacteria	4.34	±	4.06	1.04	±	1.22	4.29	±	2.97	1.47	±	1.21
Proteobacteria	9.57	±	3.70	8.07	±	4.46	13.91	±	3.18	7.56	±	5.28
Fusobacteria	0.09	±	0.12	4.47	±	8.09	0.00	±	0.00	2.30	±	3.98
Cyanobacteria	0.13	±	0.29	0.01	±	0.01	0.00	±	0.00	0.00	±	0.00
Lentisphaerae	0.00	±	0.00	0.01	±	0.01	0.00	±	0.00	0.04	±	0.06
Synergistetes	0.00	±	0.00	0.00	±	0.00	0.00	±	0.01	0.11	±	0.19

Table 3c. Intestinal microbiota by habitual intake of ghee

	Ghee n=6			Plant oil n= 9			
	mean		sd	mean		sd	p
Bacteroidetes	47.67	±	12.38	45.90	±	6.43	*0.76*
Firmicutes	33.10	±	4.10	40.45	±	10.43	*0.08*
Actinobacteria	1.55	±	0.84	3.75	±	3.64	*0.11*
Proteobacteria	10.01	±	4.50	9.38	±	4.55	*0.80*
Cyanobacteria	0.00	±	0.01	0.07	±	0.21	*0.37*
Fusobacteria	4.16	±	6.63	0.03	±	0.08	*0.08*
Lentisphaerae	0.00	±	0.00	0.01	±	0.04	
Synergistetes	0.00	±	0.00	0.04	±	0.11	

3.3 Changes of microbiota by *Panchakarma*

3.3.1 Changes by *Virechana therapy*

The order of top-six microbiota that occupied 99.8 % of microbiota at the admission did not change. These were *Bacteroidetes* (46.6%), *Firmicutes* (37.5%), *Proteobacteria* (9.6%), *Actinobacteria* (2.9%), *Fusobacteria* (1.7%) and *Verrucomicrobia* (1.5%). By *Verechana, Proteobacteria* and *Fusobacteria* increased to 32.5% and 8.1%. Respectively. At the discharge time in both *Virechana* and *Basti* treated groups, the Unassigned bacillus occupied 40.8%, and the Bacteria became 21.1%. These three occupied 93.8%. It was noteworthy that *Verrucomucrobia* became zero.

Three weeks after the discharge, the composition of the profile returned to the previous pattern. Verrucomicrobia returned to the 6th position.

Treatment-group specific change of microbiota was shown in Table 4. The remarkable changes of microbiota after the pretreatment for *Virchana* were a decrease of the *Firmicutes* and an increase of the *Proteobacteria* (p=0.012 and p=0.023, respectively). (Table 4)

The top six bacteria occupied 99.8 % at the admission. These were *Bacteroidetes* (46.6%), *Firmicutes* (37.5%), *Proteobacteria* (9.6%), *Actinobacteria* (2.9%), *Fusobacteria* (1.7%) and *Verrucomicrobia* (1.5%). By Virechana therapy, almost all cases showed a median value of 50% Bacteroides, and in one person, *Proteobacteria* occupied 96.4%. Four out of 5 cases had *Fusobacteria*, with 8.1% on average. It was noteworthy that *Verrucomucrobia* became zero by *Virchana*.

Treatment-group specific change of microbiota was shown in Table 4. The remarkable changes of microbiota after the pretreatment

Table 4. Changes of microbiota by *Virechana* and *Basti*

	Admission					Virchana						Discharge					3 W later				
	mean		sd	median	max	mean		sd	p	median	max	mean		sd	p	median	max	mean		sd	p	median	max
Bacteroidetes	46.61	±	8.90	47.48	59.48	41.02	±	22.19	*0.886*	50.92	54.44	40.77	±	18.59	*0.324*	48.72	60	49.58	±	8.66	*0.233*	46.57	69.49
Firmicutes	37.51	±	9.06	37.11	58.96	18.05	±	12.14	*0.012*	17.64	30.88	31.95	±	8.62	*0.137*	29.88	50.09	32.69	±	10.14	*0.007*	31.31	53.21
Proteobacteria	9.63	±	4.38	11.2	17.5	32.49	±	35.78	*0.023*	17.36	96.42	21.07	±	14.76	*0.022*	17.66	55.43	11.51	±	8.50	*0.376*	8.71	28.99
Actinobacteria	2.87	±	3.02	2.07	10.07	0.24	±	0.36	*0.184*	0.08	0.84	1.89	±	1.86	*0.221*	1.33	5.99	2.79	±	5.06	*0.941*	1.31	20.42
Fusobacteria	1.68	±	4.49	0	16.57	8.13	±	11.19	*0.181*	0.2	22.9	1.95	±	3.64	*0.795*	0.02	10.34	2.37	±	5.87	*0.512*	0	20.97
Verrucomicrobia	1.49	±	5.09	0	19.86	0	±	0		0	0	2.26	±	4.43	*0.42*	0	13.33	0.87	±	1.60	*0.552*	0	5.09
Cyanobacteria	0.04	±	0.17	0	0.64	0	±	0		0	0	0.013	±	0.049		0	0.19	0.12	±	0.33		0	0.99
Lentisphaerae	0.01	±	0.03	0	0.11	0	±	0		0	0	0.009	±	0.034		0	0.13	0.009	±	0.02		0	0.06
Synergistetes	0.02	±	0.09	0	0.33	0.014	±	0.031		0	0.07	0.014	±	0.054		0	0.21	0.003	±	0.01		0	0.04
Tenericutes	0.11	±	0.32	0	1.22	0	±	0		0	0	0.049	±	0.129		0	0.47	0.059	±	0.22		0	0.84
Bacteriap__TM7	0.01	±	0.02	0	0.04	0.018	±	0.04		0	0.09	0.004	±	0.008		0	0.03	0.003	±	0.007		0	0.02

for *Virchana* were a decrease of the *Firmicutes* and an increase of the *Proteobacteria* (p=0.012 and p=0.023, respectively). (Table 4)

By Virechana therapy, almost all cases showed a median value of 50% Bacteroides, and in one person, *Proteobacteria* occupied 96.4%. Four out of 5 patients had *Fusobacteria,* with 8.1% on average. It was noteworthy that *Verrucomucrobia* became zero by *Virchana*.

A decrease in *Bacteroides* and increased *Fusobacterium* were also present. *Firmicutes* returned to 36% at the time of discharge and three weeks later at home (p=0.022 and p=0.007, respectively). *Proteobacteria* returned to baseline level at a range of 4.4% to 8.7%. *Fusobacterium* dropped at the discharge but increased more than that of baseline three weeks later.

3.3.2 Changes of microbiota by *Basti* and other treatment

Basti treatment did not change the predominance of *Bacteroides* throughout treatment (47-48%). The remarkable change of microbiota by *Basti* and *Svedana* for one week was the decrease of *Firmicutes* (p=0.09) and increase of *Proteobacteria (p=0.096).*

Fusobacterium also increased but no statistical significance. After the discharge, *Proteobateria* remained high, but *Firmicutes* returned to 30% on average, ranging from 25% to 50%. Three weeks later, the variety was increased by *Fusobacterium*, *Verrucomicrobia*, *Tenericutes,* and *Lentisphaerae.*

By milk porridge therapy, a slight decrease of *Bacteroides* and *Firmicutes* was observed at the discharge. No significant changes at the phylum level occurred. Recovery of *Bacteroides*

Table 5. Changes of microbiota by Basti and other treatment

Treatment	name	Basti				milkporridge				control			
		mean	sd	median	max	mean	sd	median	max	mean	sd	median	max
Baseline	Bacteroidetes	47.273	5.649	48.38	53.92	40.500	9.871	40.5	47.48	43.355	22.804	43.355	59.48
	Firmicutes	36.017	5.94	33.29	47.56	43.175	22.323	43.175	58.96	32.380	7.835	32.38	37.92
	Proteobacteria	9.790	3.736	11.47	13.78	10.910	9.32	10.91	17.5	12.430	1.739	12.43	13.66
	Actinobacteria	3.823	3.56	2.46	10.07	4.770	3.818	4.77	7.47	1.785	0.643	1.785	2.24
	Fusobacteria	2.586	6.185	0	16.57	0	0	0	0	0.100	0.141	0.1	0.2
	Verrucomicrobia	0.261	0.412	0.07	1.02	0.360	0.339	0.36	0.6	9.93	14.043	9.93	19.86
	Tenericutes	0.227	0.459	0	1.22	0	0	0	0	0	0	0	0
	Bacteriap__TM7	0.011	0.015	0	0.03	0.025	0.021	0.025	0.04	0.015	0.021	0.015	0.03
	Bacteria	0.006	0.015	0	0.04	0.010	0.014	0.01	0.02	0.005	0.007	0.005	0.01
	Cyanobacteria	0.003	0.008	0	0.02	0	0	0	0	0	0	0	0
	Lentisphaerae	0.003	0.008	0	0.02	0.055	0.078	0.055	0.11	0	0	0	0
	Synergistetes	0	0	0	0	0.170	0.226	0.17	0.33	0	0	0	0
At discharge	Bacteroidetes3	48.420	8.802	49.92	60	35.690	11.78	35.69	44.02	49.575	0.247	49.575	49.75
	Firmicutes3	27.694	5.767	28.99	34.17	38.905	5.296	38.905	42.65	30.735	6.852	30.735	35.58
	Proteobacteria3	18.127	6.425	17.66	31.24	13.900	11.625	13.9	22.12	7.245	5.282	7.245	10.98
	Actinobacteria3	2.331	1.789	1.64	5.99	3.435	2.143	3.435	4.95	0.585	0.799	0.585	1.15
	Fusobacteria3	1.791	3.717	0	10.12	2.725	3.854	2.725	5.45	5.170	7.311	5.17	10.34
	Verrucomicrobia3	1.560	4.022	0	10.68	4.810	3.55	4.81	7.32	6.665	9.426	6.665	13.33
	Tenericutes3	0.039	0.081	0	0.22	0.235	0.332	0.235	0.47	0	0	0	0
	Bacteria3	0.003	0.008	0	0.02	0.130	0.099	0.13	0.2	0.010	0.014	0.01	0.02
	Cyanobacteria3	0.027	0.072	0	0.19	0	0	0	0	0	0	0	0
	Bacteriap__TM3	0.007	0.011	0	0.03	0	0	0	0	0.005	0.007	0.005	0.01
	Lentisphaerae3	0	0	0	0	0.065	0.092	0.065	0.13	0	0	0	0
	Synergistetes3	0	0	0	0	0.105	0.148	0.105	0.21	0	0	0	0
3 weeks later	Bacteroidetes4	48.479	7.703	46.57	61.71	42.330	0.113	42.33	42.41	60.475	12.749	60.475	69.49
	Firmicutes4	30.453	11.014	27.04	53.21	37.845	11.519	37.845	45.99	27.405	7.333	27.405	32.59
	Proteobacteria4	16.259	10.749	17.06	28.99	7.200	0.368	7.2	7.46	7.745	3.118	7.745	9.95
	Actinobacteria4	1.857	1.599	1.76	5.08	11.120	13.152	11.12	20.42	1.000	0.198	1	1.14
	Fusobacteria4	1.837	4.11	0	11.08	0	0	0	0	0.805	1.138	0.805	1.61
	Verrucomicrobia4	0.714	1.275	0	3.38	1.455	1.874	1.455	2.78	2.545	3.599	2.545	5.09
	Cyanobacteria4	0.264	0.453	0	0.99	0	0	0	0	0	0	0	0
	Tenericutes4	0.127	0.315	0	0.84	0	0	0	0	0	0	0	0
	Bacteria4	0.004	0.008	0	0.02	0	0	0	0	0	0	0	0
	Lentisphaerae4	0.003	0.008	0	0.02	0.030	0.042	0.03	0.06	0.025	0.035	0.025	0.05
	Bacteriap__TM4	0.003	0.008	0	0.02	0	0	0	0	0	0	0	0
	Spirochaetes4	0	0	0	0	0	0	0	0	0	0	0	0
	Synergistetes4	0	0	0	0	0.020	0.028	0.02	0.04	0	0	0	0

to 42% was observed three weeks later. In this group increase of *Actinobacteria* was noticeable, but no statistical significance (p=0.2). In controls, *Bacteroides* predominated but no other remarkable change.

3.4 Correlation between the phyla

Correlation between the phyla at the admission showed that *Firmicutes* showed a negative correlation with *Bacteroides* and *Verrucomicrobia*. *Verrucomicrobia* was not present in Virchana group at all and half of Basti therapy group. (Table 5)

At the time of *Virechana*, a strong correlation was present between *Proteobacteria* and *Actinobacteria* (CC 0.999, p=0.001), and *Cyanobacteria* and *Proteobacteria* (CC -0.980, p=0.02).

At the time of discharge, *Cyanobacteria* showed a positive association between *Firmicutes* (CC 0.574, p=0.025) and *Proteobacteria* (CC 0.534, p=0.04) and a negative association with *Bacteroides* (CC -0.608, p=0.016). Firmicutes also showed a positive association with Bacteria (CC 0.608, p=0.016), and with *Tenericutes* (CC 0.647 p=0.009). The strong association among *Lentisphaerae* with *Bacteria* (CC 0.904 p=0.000) and *Tenericutes* (CC0.889 p=0.000) was observed in the couple who have been treated with the milk porridge method.

The upper right shows the association of microbiota at the time of admission, and the lower-left half is the relationship between the microbiota at the entrance and three weeks after discharge.

Firmicutes, Lentisphaerae, Synergistetes, and *Bacteriap*_TM7 all showed positive association (CC 0.569 to 0.898 p=0.027 to 0.000) with *Tenericutes.*

3.5 Changes of variety of microbiota by *Panchakarma*

At the genus-specimen level, changes of microbiota profile corresponded well to the changes of phylum level. Both *Virchana* and *Basti* therapy caused increased ɣ- *Proteobacteria* (*Enterobacteriaceae*)(10-20%), *Prevotalla copri, and Lachnospiraceae (3- 5%).* Akkermancia

Table 6. Correlation analysis between microbiota at baseline and three weeks later.

3 Ws later \ Admission		Bacteria	Actinobacteria	Bacteroidetes	Cyanobacteria	Firmicutes	Fusobacteria	Lentisphaerae	Proteobacteria	Synergistetes	Bacteriap_TM7	Tenericutes	Verrucomicrobia
Bacteria	P's CC	0.294	0.313	-0.044	-0.118	0.065	-0.151	0.355	-0.011	0.374	.663**	-0.146	-0.082
	probability	0.287	0.256	0.875	0.674	0.817	0.592	0.194	0.969	0.17	0.007	0.604	0.771
Actinobacteria	P's CC	0.146	0.444	0.169	-0.182	-0.447	-0.142	-0.121	0.216	-0.061	0.164	-0.228	-0.132
	probability	0.604	0.097	0.546	0.517	0.095	0.613	0.669	0.44	0.829	0.558	0.413	0.638
Bacteroidetes	P's CC	-0.197	-0.015	0.448	0.246	-.629*	-0.082	-0.433	-0.017	-0.407	0.047	-0.162	-.630*
	probability	0.483	0.957	0.094	0.376	0.012	0.773	0.107	0.952	0.132	0.869	0.564	0.012
Cyanobacteria	P's CC	-0.071	-0.122	0.207	-0.082	0.012	-0.075	-0.087	-0.255	-0.076	-0.205	-0.094	-0.082
	probability	0.801	0.664	0.459	0.772	0.967	0.79	0.758	0.36	0.787	0.463	0.739	0.771
Firmicutes	P's CC	-0.092	-0.233	-0.503	0.199	.817**	-0.109	.708**	-0.443	.647**	0.081	0.315	0.025
	probability	0.745	0.403	0.056	0.477	0	0.699	0.003	0.098	0.009	0.773	0.253	0.93
Fusobacteria	P's CC	.805**	-0.199	-0.143	.649**	-0.075	.734**	-0.122	-0.444	-0.107	-0.274	-0.132	-0.064
	probability	0	0.477	0.61	0.009	0.79	0.002	0.665	0.098	0.704	0.323	0.639	0.82
Lentisphaerae	P's CC	-0.116	-0.03	-0.292	0.009	0.463	-0.132	.700**	-0.338	.983**	0.508	0.083	-0.062
	probability	0.68	0.916	0.291	0.975	0.082	0.64	0.004	0.218	0	0.053	0.77	0.825
Proteobacteria	P's CC	-0.27	.538*	0.092	-0.293	-0.396	-0.435	-0.029	0.383	-0.321	0.116	0.017	0.236
	probability	0.33	0.039	0.744	0.29	0.144	0.105	0.919	0.159	0.243	0.681	0.951	0.397
Synergistetes	P's CC	-0.102	-0.024	-0.237	-0.108	0.361	-0.115	.722**	-0.153	-0.041	.546*	-0.094	-0.051
	probability	0.718	0.934	0.396	0.702	0.186	0.682	0.002	0.587	0.884	0.035	0.739	0.857
Bacteriap_TM7	P's CC	-0.017	-0.005	-0.037	-0.291	-0.187	-0.263	0.249	0.444	-0.012	-0.291	-0.142	-0.183
	probability	0.952	0.985	0.897	0.294	0.504	0.343	0.372	0.097	0.965	0.292	0.613	0.514
Tenericutes	P's CC	-0.126	0.107	-0.37	.579*	0.468	-0.142	-0.156	-0.141	-0.091	.634*	0.284	-0.1
	probability	0.656	0.704	0.174	0.024	0.078	0.613	0.579	0.617	0.747	0.011	0.305	0.724
Verrucomicrobia	P's CC	-0.044	-0.111	0.043	-0.073	-0.004	-0.099	.599*	-0.047	-0.075	-0.116	-0.086	.771**
	probability	0.875	0.695	0.878	0.796	0.99	0.725	0.018	0.869	0.791	0.68	0.761	0.001

muciniphila increased at discharge in the milk porriage and *Basti* group.

The number of species more than 1.0% at baseline was 26, while it decreased to 18 during *Virchana* and 24 after *Basti,* then it became 22 at the discharge, and increased to 27 after three weeks. It may correspond to the diversity of microbiota. (Table 7)

ASV number and Shannon's index showed corresponding change. One patient showed a marked predominance of *Proteobacteria* up to 96% during Virchana.

4 Discussion

Ayurveda is a system of medicine with historical roots in the Indian subcontinent[1-4]. Globalized practices derived from Ayurveda traditions are included in a type of alternative medicine[3,21]. It is said that Ayurveda medicine does not have a scientific basis, so it is often deemed pseudoscientific or trans-science system. Ayurvedic medicine's central concept is the theory that health exists when there is a balance between the three fundamental bodily bio-elements (*doshas*) called *Vata*, *Pitta*, and *Kapha*.

Panchakarma therapy aims to eliminate excessive *Doshas* from the body to maintain the state of health for a longer duration. *Virechana therapy* is one of the *Panchakarma* therapies wherein detoxication is done by drugs and oil to exclude liposoluble toxins. It specifically aims to eliminate excessive *Pitta Dosha* from the body. It is said to be beneficial for detoxication in skin disorders, abscesses, and liver disorders because *Pitta* is considered to control metabolism. Rais[10] conducted the study to evaluate *Virechana* therapy's effect on serum electrolytes in 15 people and ascertain the safety of therapeutic purgation.

Table 7. Microbiota profile by genus-species level

Table 7. Microbiotic profile by genus species level																							
Baseline n=15				Verchana n=5				Bast n=7				at discharge n=15				3 weeks later n=14							
	mean		sd		median		mean		sd		median		mean		sd		median		mean		sd	
Bacteroides	21.21	±	8.08	Bacteroides	23.26		19.93	±	15.58	17.96	Bacteroides		25.14	±	6.70	37.48	Bacteroides		19.20	±	10.85	22.19	Bacteroides		22.34	±	12.19
Bacteroides plebeius	5.35	±	11.42	Klebsiella	0.01		18.96	±	40.79	0.56	Enterobacteriaceae		9.56	±	9.57	25.79	Enterobacteriaceae		13.15	±	16.94	9.89	Bacteroides plebeius		5.43	±	11.48
Faecalibacterium prausnitzii	4.37	±	2.78	Enterobacteriaceae	3.67		8.57	±	6.06	12.04	Bacteroides uniformis		6.72	±	3.85	11.07	Prevotella copri		4.61	±	10.56	0.09	Lachnospiraceae		4.57	±	4.91
Lachnospira	4.18	±	3.01	Prevotella copri	3.46		7.64	±	12.69	0.89	Lachnospiraceae		4.54	±	2.80	8.19	Clostridiaceae		3.97	±	12.88	0.06	Bacteroides fragilis		4.39	±	14.77
Bacteroides uniformis	3.73	±	2.74	Lachnospiraceae	3.36		5.00	±	3.83	6.14	Lachnospira		3.08	±	2.97	8.75	Bacteroides uniformis		3.92	±	3.82	2.73	Faecalibacterium prausnitzii		3.91	±	2.76
Ruminococcaceae	3.43	±	2.60	Fusobacterium	2.37		3.55	±	7.81	0.05	Bacteroides ovatus		3.04	±	2.72	7.40	Bacteroides plebeius		3.29	±	8.53	0.02	Bacteroides uniformis		3.67	±	2.41
Rikenellaceae	3.21	±	2.91	Bacteroides caccae	2.55		2.79	±	5.34	0.05	Faecalibacterium prausnitzi		2.93	±	3.58	10.35	Lachnospiraceae		3.18	±	2.76	2.76	Lachnospira		3.25	±	2.81
Enterobacteriaceae	3.19	±	4.49	Roseburia	0.60		2.70	±	2.72	2.41	Sutterella		2.77	±	1.31	4.92	Akkermansia muciniphila		2.47	±	4.39	0.10	Rikenellaceae		3.14	±	3.56
Lachnospiraceae	3.16	±	1.34	Phascolarctobacterium	2.74		2.66	±	2.43	2.35	Rikenellaceae		2.65	±	2.46	6.87	Phascolarctobacterium		2.44	±	2.95	0.98	Ruminococcaceae		2.49	±	2.59
Phascolarctobacterium	2.75	±	2.64	[Prevotella]	1.64		2.64	±	5.83	0.06	Bacteroides plebeius		2.41	±	4.63	12.09	Sutterella		2.43	±	1.38	2.83	Citrobacter		2.35	±	6.22
Sutterella	2.51	±	1.65	Fusobacteriaceae	2.43		2.35	±	5.25	2.35	Akkermansia muciniphila		2.02	±	4.01	10.68	Faecalibacterium prausnitzii		2.35	±	2.92	1.28	Oscillospira		2.14	±	1.71
Oscillospira	2.43	±	1.99	Fusobacteriaceae	1.97		2.23	±	5.00	2.23	Phascolarctobacterium		1.86	±	2.42	6.45	Lachnospira		2.17	±	2.52	1.82	Bifidobacterium adolescentis		2.07	±	5.34
Prevotella copri	2.38	±	6.97	Citrobacter	0.01		1.75	±	3.13	0.21	Bacteroides caccae		1.72	±	1.99	5.32	Peptostreptococcaceae		2.16	±	8.22	0.02	Sutterella		2.03	±	1.45
Ruminococcus	1.99	±	3.48	Dialister	0.36		1.26	±	2.56	0.16	Klebsiella		1.51	±	3.03	8.27	Bacteroides ovatus		1.74	±	2.23	1.13	Phascolarctobacterium		1.96	±	2.09
Bacteroides ovatus	1.96	±	1.57	Sutterella	1.28		1.16	±	1.49	0.77	Oscillospira		1.50	±	1.07	3.52	Klebsiella		1.74	±	3.10	0.47	Bacteroides ovatus		1.95	±	1.92
[Barnesiellaceae]	1.65	±	1.69	Roseburia faecis	1.12		1.09	±	1.51	1.18	Ruminococcaceae		1.48	±	1.04	2.64	Megasphaera		1.65	±	3.54	0.06	Enterobacteriaceae		1.94	±	4.07
Parabacteroides	1.58	±	1.59	Bacteroides fragilis	1.44		1.03	±	2.01	0.14	Parabacteroides		1.46	±	1.46	4.37	Rikenellaceae		1.63	±	2.00	1.20	Parabacteroides		1.74	±	1.73
Bacteroides caccae	1.57	±	2.27	Bacteroides ovatus	0.12		1.02	±	0.81	1.49	[Barnesiellaceae]		1.44	±	1.15	2.88	Megamonas		1.62	±	5.52	0.00	α - proteobacteria		1.67	±	3.30
Akkermansia muciniphila	1.49	±	5.09	0.05							α - proteobacteria		1.43	±	3.20	8.62	Ruminococcaceae		1.45	±	1.47	0.80	Klebsiella		1.48	±	2.47
Bifidobacterium adolescentis	1.35	±	2.32	0.13							Acidaminococcus		1.35	±	1.87	4.72	Bacteroides caccae		1.27	±	1.84	0.80	Parabacteroides distasonis		1.44	±	2.10
Roseburia faecis	1.22	±	2.58	0.18							Prevotella		1.26	±	2.47	6.59	Parabacteroides		1.21	±	1.43	0.59	Ruminococcus		1.41	±	2.35
Parabacteroides distasonis	1.08	±	1.27	0.83							Morganella morganii		1.17	±	3.01	7.99	Oscillospira		1.01	±	1.02	0.63	Fusobacteriaceae		1.27	±	3.28
Streptococcus	1.08	±	2.92	0.04							Veillonella		1.15	±	3.04	8.04							Acidaminococcus		1.24	±	3.08
α proteobacteria	1.03	±	1.74	0.87							Bifidobacterium		1.11	±	1.83	4.63							Coprococcus		1.22	±	1.76
Blautia	1.02	±	1.53	0.54																			Bacteroides caccae		1.18	±	2.22
Roseburia	1.01	±	1.31	0.45																			[Barnesiellaceae]		1.15	±	1.03

The current study focused on the changes in intestinal microbiota before and after the *Panchakarma*, and the results were satisfactory to show clinical improvement. Each participant received *Virechana, Basti*, or milk porridge sudation therapy according to their condition. A personalized plan has carefully scheduled the right selection of oil, sweating, massage, and laxatives or meditation and mindfulness. All symptoms became lighter, especially with skin eruptions. Participants who took part in the trial also got mental settlement to develop a calm mind. All 13 patients showed improvement of skin rash, depression, and other symptoms.

The diet in the present camp was the modified Japanese style. They preferred vegetarian food basically, and brown rice eaters showed healthy bowel movement in conjunction with intestinal microbiota[22]. Bodyweight loss seemed to occur only by *Virechana* therapy, but as the body fat increased in all, the non-fatty mass had also decreased by *Basti* therapy.

4.1 Changes in Microbiota and clinical manifestation

The present participants showed dominancy of *Bacteroidetes* than *Firmicutes*. Most Japanese showed dominancy of *Firmicutes*[22]. It was reflected in their dietary habits, mostly vegetarian way. Vegetarians seemed to have more *Bacteroides*, *Firmicutes,* and *Actinobacteria* than omnivores who had more *Proteobacteria, Fusobacteria,* and *Cyanobacteria*. Chandhar et al [23] analyzed 18 healthy people and found different bacterial profiles by Prakriti (constitution of a person), by Vata, Pitta, and kappa. In this series, Bacteroides, Desulfovibrio, slackia, and succinivibrio were common.

Kind of staple foods were five polished white rice, four white rice and barley, three mixtures of white rice and brown rice, and three genmai (brown rice). Genmai eaters showed fewer *Actinobacteria* and *Proteobacteria*, but the "white rice+barley" group also showed a similar trend. Significant difference among groups was not present because of the small number of cases. When the groups were divided by oil consumption, ghee users showed higher *Fusobacterium* and less *Firmicutes* and *Actinobacteria*.

Panchakarma observed the remarkable changes of the microbiota. After the pretreatment for *Virechana* therapy, a decrease of *Firmicutes* and increase of *Proteobacteria* were noticed. *Bacteroides* predominated between 47-48% throughout the treatment.

The change of microbiota by *Basti* and *Swedana* for one week was also the decrease of *Firmicutes* and increase of *Proteobacteria*. After the discharge, *Firmicutes* returned to 30% on average, ranging from 25% to 50%. *Proteobacteria* returned to baseline level at a range of 4.4% to 8.7% three weeks later. *Fusobacterium* also increased but no statistical significance. Three weeks after discharge, the variety was increased by *Fusobacterium*, *Verrucomicrobia*, *Tenericutes,* and *Lentisphaerae*.

Watanabe et al.[12] reported microbiota of 109 healthy people and noted that standard bacterial profiles at the phylum level were 44.3±9.9% *Firmicutes*, 20.7±8.8% *Bacteroides*, 8.3±6.3% *Actinobacteria*, 1.7±2.7% *Proteobacteria,* and 1.2±4.2% (max 39.4%) *Verrucobacteria*.

Their series's dietary habit was mostly brown rice eaters, so they showed a certain characteristic profile. At the genus level, 12.7% *Bacteroides*, 8.3% *Blautia*, 7.9% *Faecalibacterium*, 6.3%*Bifidobacterium,* 5.3%*Prevotella,* 4.9%*Eubacterium,* 3.8% *Ruminococcus,* 2.6% *Fusicatenibacter,* 1.9%*Collinsella,* 2.4% *Streptococcus,* 2.1% *Subdoligranulum,* 1.7% *Anaerostipes,* 1.2% *Akkermansia* and 1.7% *Roseburia* occupied more than 1%. The difference between the brown rice and white rice eaters by microbiota profile was high butyrate-producing bacteria and low fusobacterium.

The distribution of butyrate-producing bacteria among *Firmicutes* phylum seemed to be uneven[25]. Butyrate was not only produced from dietary fiber but lactate. Barley dietary fiber may have a similar effect on microbiota because white rice+Barley showed a similar profile with *genmai*.

The subjective feelings of well having complex determinants and butyrate-producing bacteria could be added among them[12]. We have identified a possible correlation between a high personal sense of health and the presence of butyric acid-producing bacteria in the gut. Besides, increased *Enterobacteriaceae* in

γ-*Proteobacteria* may produce β-hydroxybutyrate, which yield happy feeling in the brain is a common phenomenon in fasting[26,27].

A weakness of the present study. This was a pre and post therapy study on the relationship between Ayurveda *Panchakarma* and intestinal microbiota changes. Ayurveda therapy is based upon the tailor-made approach, so it does not fit the ordinary RCT. Accumulation of cases would make new evidence of patient-centered-therapy or narrative medicine. Pre and post-tests would be useful on such occasions[28]. Four significant phyla, *Firmicutes, Bacteroidetes, Proteobacteria,* and *Actinobacteria,* were present in all, but other phyla were less current, so the statistical power was insufficient. Decreased *Firmicutes* and increased *Proteobacteria*, and loss of *Verrucomicrobia* were commonly present in all participants, but these changes were usually considered to be worse for health, so more accumulation of clinical cases and long observation is necessary[29]. Changes in bacterial profile would occur by repeated irrigation, which changed the enteroenvironment and many metabolic changes. Laboratory tests were not

done at this time, so we could not measure the concentration of short-chain fatty acids and β- hydroxybutyrate, which has a mental effect. A more large number of cases and integrated studies should be done in the future.

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Declarations:

The authors declare that they have no conflicts of interest, that the work has been approved by the ethics committee responsible in the workplace. The research was done with funds provided by The Lifescience Promoting Association.

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RESUMEN

Introducción: Se han analizado terapias ayurvédicas y prácticas médicas para un grupo de pacientes en Japón. La característica del tratamiento ayurvédico es una desintoxicación con una gran cantidad de tratamiento con aceite mediante un masaje con aceite en la superficie del cuerpo y una terapia de purificación con ghee o aceite de hierbas especialmente preparado. Los cambios de la microbiota intestinal durante estos tratamientos no han sido bien estudiados. Mé-

todo: Los participantes fueron reclutados de la Clínica Hatai Ayurveda en Tokio. La terapia de Virechana, una terapia de purificación o la terapia de Basti (decocción y enema de aceite) se llevó a cabo en 13 pacientes con diversas manifestaciones. Todos los participantes proporcionaron el detalle de su estilo de vida, hábitos dietéticos, enfermedades pasadas y presentes mediante el cuestionario, y se registró la condición precisa durante la admisión al final del campamento. Se tomaron muestras fecales a la entrada, durante el tratamiento, al alta y tres semanas después para analizar la microbiota intestinal por el gen seqyebcubg 16srRNA. Resultados: el peso corporal disminuyó aproximadamente un 5% con la terapia de Virechana, mientras que no ocurrió con Basti, pero la grasa corporal aumentó un 4% (2,2 kg) en promedio en ambos grupos. Varias manifestaciones clínicas de los participantes mejoraron, especialmente en una erupción cutánea y un cambio atópico. El paciente deprimido también remitió mejoras en sus ganas de vivir. En su mayoría son vegetarianos y tenían más Bacteroides (48.09 ± 7.51%), Firmicutes (38.27 ± 10.82%) y Actinobacteria (3.30 ± 3.58%) que los omnívoros que tenían más Proteobacteria (10.73 ± 4.75%), Fusobacteria (2.40 ± 6.25%) y cianobacterias (0,09 ± 0,24%). Cuando los grupos se dividieron por el consumo de aceite, los usuarios de ghee mostraron más Fusobacterium y menos Firmicutes y Actinobacteria. La terapia con Virechana provocó cambios notables en la microbiota después del pretratamiento, como la disminución de Firmicutes y el aumento de Proteobacterias. A nivel género-especie, destacan el aumento de Enterobacteriaceae y la pérdida de Akkermansia municiphila. Niruha Basti y Matra Basti disminuyeron Firmicutes y aumentaron Proteobacteria (p = 0.096). Fusobacterium también aumentó. Después del alta, la Proteobateria se mantuvo alta, pero Firmicutes regresó al 30% en promedio, oscilando entre el 25% y el 50%. Tres semanas después, la variedad aumentó con Fusobacterium, Verrucomicrobia, Tenericutes y Lentisphaerae. La variedad de especies también aumentó tres semanas después. **Conclusión**: Varias quejas de los participantes mejoraron por el tratamiento ayurvédico con una gran cantidad de tratamiento de aceite por masaje de aceite de superficie corporal y terapia de purga. Causó cambios en la microbiota intestinal y los metabolitos bacterianos pueden afectar las lesiones cutáneas y la salud mental como la sensación depresiva.

Oral Manifestations and Olfactory and Gustatory Dysfunction in Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-Cov-2 Virus) Disease: A Systematic Review

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ABSTRACT

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2 virus) disease had first appeared in December 2019 in Wuhan, China and has been spreading quickly throughout the world since then. Since then, the outbreak of this severe viral disease has become a global threat to humanity. An early diagnosis and isolation are the most significant measures required to prevent its spread. Recent anecdotal evidence has suggested oral manifestations with or, without olfactory and gustatory impairment in association with corona virus disease (COVID-19). Angiotensin converting enzyme-2 (ACE-2) is expressed in oral mucosa in large amounts and can, thus, contribute in the early manifestations of this deadly viral disease. The oral manifestations of corona virus disease can occur in the form of irregular ulcerative lesions in relation to different parts of the oral cavity and particularly, in relation to the attached mucosa in the hard palate region as well as inflammation and subsequent, atrophy of the various tongue papilla. The associated olfactory and gustatory dysfunction can, also, lead to partial and/or, even a complete loss of the ability to smell and taste in the early stages of the disease onset. Evidence has, also, suggested the presence of SARS-CoV-2 nucleic acid in human saliva making it the carrier of the infectious viral disease as well as aiding in its diagnosis. We have systemically searched medical database for the same and have reviewed all the literature available up to 29th of June 2020.

Key words: Oral manifestations, olfaction, gustatory dysfunction, severe acute respiratory syndrome corona virus 2 (SARS-CoV-2 virus) disease, corona virus disease (COVID-19)

Introduction

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2 virus) is responsible for causing corona virus disease (COVID-19). Since its outbreak, this deadly, infectious disease has become a serious global threat infecting 1,00,55,037 people worldwide while 4,99,892 deaths have been reported till date. In India alone, 16,095 deaths with 5,28,859 people infected have been reported till date.[1] SARS-CoV-2 has its roots from Nidovirus family and shares 96.2% genetic similarities with the corona virus found in bats, thus, hypothesized to be possessing a possible zoonotic origin.[2,3] It is, also, postulated that bat corona virus might have undergone Homologous Recombination with some intermediate host and has developed the ability to infect humans. The virus mainly spreads via droplets from an infected patient, but can, also, spread through direct contact and orofaecal route.[4] Viral genome studies of 103 samples suggest that around 30% of them were infected with S-type while the rest, with L-type subtypes of SARS-CoV-2 virus.[4] The possible binding of the virus spike protein (a surface glycoprotein) to the angiotensin-converting enzyme-2 (ACE-2) expressed in the host cells is considered to be the major factor in the pathogenesis of the viral disease.[5] This is the reason as to why the respiratory manifestations are reported commonly amongst the

infected hosts as Type 2 pneumocytes present in the lungs express the said enzyme in large amounts while the infected patients develop pneumonia-like symptoms including shortness of breath, dry cough followed by high fever and in later stages, acute respiratory distress syndrome (ARDS) with numerous other secondary complications as multiple organ failure. In addition, upper respiratory manifestations including nasal congestion and sore throat are commonly observed in patients exhibiting mild disease.[6] Since the virus accesses host cells via the enzyme angiotensin-converting enzyme-2 (ACE-2), there has been evidence that the superficial stratified epithelial cells of the oesophagus, absorptive enterocytes from the ileum and colon, cholangiocytes, myocardial cells, proximal tubular cells from the kidneys and urothelial cells from the bladder, also, act as important areas where an active infection can be seen since they all express high amounts enzyme ACE-2.[7] The analysis of public bulk-seq RNA datasets suggest that the mucosa of oral cavity, also, expresses the same enzyme ACE2 found in higher concentrations in the tongue than other oral sites as compared to the gingival tissues and cells of the buccal mucosa and can, thus, lead to active manifestations of this deadly viral disease in the early stages of infection.[7] Therefore, there might be a high probability or, possibility that oral mucosa as well and organs excluding lungs are, also, at risk for secondary sites of infection in the pathogenesis of the disease process. In a mice model, this has been further emphasized based on the observation that SARS-CoV-2 virus can enter via olfactory bulbs, as well.[8] Some of the published literature reports the cutaneous and systematic manifestations of COVID-19 disease in detail, there is a paucity of data, though, in relation to the oral manifestations of this infectious disease with oral mucosa being a possible source of infection acting as a reservoir for the virus in clinically occult cases. Fewer studies, though, on limited available evidence have reported oral signs and symptoms and olfactory and gustatory dysfunction in the early stages of the disease process prior to the actual symptoms or, even, in asymptomatic cases. Few reports have, also, indicated that oral signs and symptoms can be independent of olfactory and gustatory dysfunction and *vice versa* or, can manifest simultaneously. The present review is based on a systematic search of the available medical database on similar lines until 29th of the June, 2020.

Materials and Methods

The present review was based on a systematic search of PubMed, Google Scholar and Elsevier data base up till 29th of the June, 2020 with key words oral manifestations*/signs*/symptoms of and olfactory and gustatory dysfunction in COVID-19 disease. Quick readings of abstract were conducted and articles of significant importance were kept for review. In addition, we, also, accessed and retrieved the cross references which seemed to be clinically relevant. Articles written exclusively in Chinese were excluded while all the original articles, letters to the editor, case reports and reviews in English literature were included for the review.

Discussion

SARS-CoV-2 virus is a positive single strained ribonucleic acid wrapped in a nucleoprotein (N). The viral envelop (E) surrounds this helical nucleocapsid while the matrix protein (M) is embedded in the viral envelope. Spike (S) protein is responsible for attaching, fusing and infecting particular host cells and this forms the pathogenesis of this highly contagious disease process. Several of beta corona viruses, also, possess hemagglutinin esterase protein.[9] RNA genomes code for 4 structural protein (E, N, S, M) and one for viral replication/transcription (RNA dependent RNA polymerase, RdRp).[9] The virus S glycoprotein attaches to the enzyme angiotensin-converting enzyme-2 (ACE-2) expressed in the various host cell types including various organs such as lungs, kidney, heart, gastrointestinal tract and oral mucosa, this facilitates the entry of virus into the host body.[9] The entry and binding processes are, then, followed by fusion of the viral membrane and host cell membrane.[11] After fusion

occurs, the Type 2 transmembrane serine protease (TMPRSS2) that is present on the surface of the host cell membrane clears the enzyme ACE2 and activates the receptor-attached spike-like, S protein.[12] Once entered in cell, the viral genome (mRNA) is ready for translation and uses the RNA dependent RNA polymerase for its synthesis.[12] Since, the oral mucosa could, also, express enzyme ACE2, chances of oral manifestations, alternation in ability to taste and smell cannot be denied.[7]

In a letter editor, it has been stated that SARS-CoV-2 RNA can be detected in the saliva of the infected host before lung lesions appear.[13] Vinayachandran and Balasubramanian[14], also, reported possible oral symptoms including hypogeusia, xerostomia and chemosensory alterations in the infected hosts. Previously, an experiment in Rhesus Macaques has, also, demonstrated that the initial target of SARS virus is the epithelial lining of the salivary glands.[15] Mucosal involvement includes viral exanthems composed of diffuse erythema, petechiae and pustule formations.[16] Lechien et al[17], in their study, also, observed the prevalence of olfactory and gustatory dysfunction to be 24.2% in patients presenting with mild COVID-19 disease. Evidence has, also, suggested that 95.8% of the infected hosts of COVID-19 disease present with the symptom of anosmia. In addition to anosmia, the other common manifestations of COVID-19 disease include ageusia as well as dysgeusia which, too, have been reported frequently. The possible explanation behind anosmia seen as a manifestation of COVID-19 disease could be due to viral involvement in central nervous system (CNS) causing damage to nasal ducts as well as the local tissues effecting olfaction, the exact phenomenon behind this, though, remain unclear.

Another possibility behind the olfactory and gustatory dysfunction seen as manifestations of COVID-19 disease is due to the SARS-CoV-2 virus entering via the olfactory nerve or, peripheral trigeminal nerve carrying the infection to the CNS, thus, potentially damaging the trigeminal nerve into the CNS, thereby, causing dysosmia and dysgeusia. Existing literature, also, suggests that Epstein-Barr virus and some of the corona viruses may cause smell and taste diseases. In addition, upper respiratory tract infections due to the virus can induce a permanent disorder leading to a partial or, complete loss of the olfactory senses. Fewer studies have, also, suggested that post-infections, anosmia can be stabilised.[8,18,19]

The oral manifestations have already been seen as an indicator of several systemic diseases. Oral cavity may exhibit manifestations in the form of oral ulcerations, gingival bleeding, glossitis, oral pain or, halitosis. Viral infections usually manifest either as superficial and deep oral ulcerations or, vesicle formations in relation to the various parts of the oral mucosa depending upon the severity of the infection and area of invlolvement.[20-22] In a case series published by Martín Carreras-Presas et al[23], out of 3 patients including 2 suspects and one confirmed case of SARS-CoV-2 infection, case 1 presented with multiple orange-colored ulcers with an erythematous halo and symmetric distribution on the right hard palate of the patient, case 2 presented with multiple pinpoint yellowish ulcers with an erythematous halo on the left hard palate of the patient while case 3 reported that the lesions were more pruritic than painful. The said patient presented with 3 vesicles on the inner lip mucosa with the vesicular lesion located closer to the right commissure being intact and tense suggest oral vesiculo-bullous lesions to be one of the marked features in SARS-CoV-2 infection.

On elicitation of the case history, the first patient was a 56 years old, healthy male patient and he had, also, reported pain, dysgeusia and enlargement of lymph nodes before the onset of intra-oral lesions. The 2nd patient among these three was 58 years old, male with a positive history of diabetes mellitus (DM) with hypertension (HT). He, also, reported the oral lesions to be painful. Interestingly, in last case of confirmed COVID-19 infection, initially, the female patient, a sufferer of co-morbidities in the form of obesity with HT, she had reported pain on tongue while cutaneous manifestations were, also, observed followed by vesicles in her inner lip mucosa as well as desquamative gingivitis. In the 3rd patient, co-morbidities were considered to have triggered ulcerative/herpetic-like lesions in relation to the hard plate. Not to for-

get, all the said three patients were in a period of lock down that might have contributed to a psychological breakdown, too, with stress and anxiety arising due to the recent pandemic leading to such characteristic oral manifestations. Furthermore, in the last case of confirmed COVID-19 infection, lesions appeared a week post discharge, thereby, making the clinicians conclude that oral manifestations associated with SARS-CoV-2 might have nothing to do with the active SARS-CoV-2 infection per se. (Table 1)

In another case reported by Ciccarese et al[24] where a 19 years old female was a confirmed case of SARS-CoV-2 infection, the patient reported cutaneous and oral manifestations including hyposmia and oro-pharyngeal lesions on the 7th day of onset of symptoms. The characteristic findings in the said patient included a sudden onset of anosmia with asymptomatic cutaneous and oro-pharyngeal lesions which later evolved into frank oral erosions and ulcerative lesions with encrustations on the inner surface of the lips, palatal and gingival tissues and petechiae. (Table 1) Interestingly, Soares et al[25] reported not only the oral clinical manifestations in a confirmed SARS-CoV-2 patient with a known history of DM and HT but, also, stated the histopathology of oral lesions in a 42 years old male patient. The said patient had reported painful ulceration in the buccal mucosa while further examination revealed that besides the ulcerated lesions, multiple reddish macules of different sizes were scattered along the hard palate, tongue and lips. (Table 1)

In a similar case study of another 51 years old male patient published by Cebeci Kahraman and Çaşkurlu[16] who was, also, a confirmed SARS-CoV-2 patient, the patient presented oral symptoms on the 10th day after onset of symptoms when the sore throat symptoms worsened 10 days after the onset of symptoms. Also, in the same patient, oral examination revealed a large erythematous surface in the oropharynx and on the hard palate while few petechiae in the midline and numerous pustular exanthems near the soft palate which were more prominent on the left side and ranged from 1-3 mm in diameter. (Table 1) Another interesting finding in the said patient was that the patient had reported altered olfactory and gustatory functions before the onset of frank oral and oro-pharyngeal lesions. (Table 1) Ansari et al[26], in his literature review of two confirmed SARS-CoV-2 patients including a 56 years old female and 75 years old male patients, also, described ulcers on hard palate while ulcers with an erythematous background on the anterior aspect of dorsal surface of tongue on 5th and 7th day of onset of active SARS-CoV-2 infection. A histo-pathological examination, also, confirmed the findings observed clinically in the said patients. (Table 1)

In a Brazilian case reported by Amorim Dos Santos et al[27] of a 67 years old Caucasian male patient with a known history of coronary artery disease (CAD), autosomal polycystic kidney disease, systemic hypertension and kidney transplant, the patient was on immunosuppressants and pharmacological prophylaxis for venous pulmonary thrombo-embolism, the patient presented with a persistent white plaque on the dorsal aspect of tongue with multiple pinpoint yellowish ulcers on the dorsal surface of tongue resembling ulcers seen in the late stage of recurrent intra-oral herpes. A nodule was, also, observed in the lower lip suggesting a reactive fibroma measuring approximately 1 cm in its largest diameter. The said authors, though, failed to mention regarding the onset of the said manifestations as there was a high probability of the lesions being reactive in nature to the drugs taken rather than being associated with the active SARS-CoV-2 infection per se. (Table 1) In another case reported by Chaux-Bodard et al[28], painful inflammation of tongue papilla followed by erythematous macules which further evolved into irregular ulcers were observed in a 45 years old female patient confirmed as SARS-CoV-2 infected on the 4th day of onset of the infection. (Table 1) (For full information on oral manifestations of SARS-CoV-2 infection, see Table 1)

Likewise, both olfactory and gustatory dysfunction have been considered to be one of the recently reported symptoms seen in increasing numbers in patients infected with SARS-CoV-2 virus. In a recent report by *Gane* et al[29], it was mentioned that a 48 years old male patient experienced sudden onset anosmia without

Table 1: Oral manifestations of SARS-CoV-2 infection

First Author/ Reference	Sample size & Diagnostic status of SARS-CoV-2	Past History	Days of onset of oral and related symptoms	Oral manifestations
Martín Carreras-Presas et al[23]	Total 3 patients; 2 of them were suspects while one confirmed SARS-CoV-2 patient.	Case 1: Healthy; Case 2: Diabetic with hypertension; Case 3: Obese with hypertension.	--	Case 1: Multiple orange-colored ulcers with an erythematous halo and symmetric distribution on the right hard palate of the patient; Case 2: Multiple pinpoint yellowish ulcers with an erythematous halo on the left hard palate of the patient; Case 3: The patient reported that the lesions were more pruritic than painful. The patient presented with 3 vesicles on the inner lip mucosa with the vesicular lesion located closer to the right commissure intact and tense.
Ciccarese et al[24]	One confirmed SARS-CoV-2 patient.	None.	2 days before being admitted in hospital.	Sudden onset of anosmia, asymptomatic cutaneous and oro-pharyngeal lesions. Oral findings included oral erosions and ulcerative lesions with encrustations on the inner surface of the lips, palatal and gingival tissues and petechiae.
Soares et al[25]	One confirmed SARS-CoV-2 patient.	Diabetes with hypertension.	--	Painful ulceration in the buccal mucosa. Oral examination revealed that besides the ulcerated lesions, multiple reddish macules of different sizes were scattered along the hard palate, tongue and lips.
Cebeci Kahraman and Çaşkurlu[16]	One confirmed SARS-CoV-2 patient.	None.	10th day of onset.	Sore throat symptoms worsened 10 days after the onset of symptoms. Oral examination revealed a large erythematous surface in the oropharynx and on the hard palate, few petechiae in the midline and numerous pustular exanthems near the soft palate which were more prominent on the left side and ranged from 1-3 mm in diameter.
Ansari et al[26]	Two confirmed SARS-CoV-2 patients.	None.	5th day of onset. 7th day of onset.	Ulcers on hard palate. Ulcers with an erythematous background on the anterior aspect of dorsal surface of tongue.
Amorim Dos Santos et al[27]	One confirmed SARS-CoV-2 patient.	Coronary artery disease (CAD); Autosomal polycystic kidney disease; Systemic hypertension; Kidney transplant; On immunosuppressants and pharmacological prophylaxis for venous pulmonary thrombo-embolism).	--	A persistent white plaque on the dorsal aspect of tongue. Other oral findings included multiple pinpoint yellowish ulcers on the dorsal surface of tongue resembling ulcers seen in the late stage of recurrent intra-oral herpes. A nodule located in the lower lip measuring approximately 1 cm in its largest diameter.
Chaux-Bodard et al[28]	One confirmed SARS-CoV-2 patient.	None.	4th day of onset.	Painful inflammation of tongue papilla followed by erythematous macules which further evolved into irregular ulcers.
Jimenez-Cauhe ***et al***[46]	21 confirmed SARS-CoV-2 patients. Evidence of skin rashes. Out of these, 6 developed viral exanthems. Data of six patients with oral cavity rashes. Age range 40-69 years.	None.	Case 1: 12th day; Case 2: 2nd day; Case 3: 19th day; Case 4: 24th day; Case 5: 2nd day; and Case 6: 19th day of onset.	Types of viral exanthems observed: Case 1: Macules; Case 2: Petechiae; Case 3: Macules with petechiae; Case 4: Macules with petechiae; Case 5: Petechiae; and Case 6: Macules with petechiae.
Chen et al[30]	Total of 108 validated questionnaire participants. No. of males and females being 52 and 55 respectively.	None.	--	Oral manifestations with their respective % of involvement in patients: **Amblygeustia:** 51 (47.2%); Dry mouth: 50 (46.3%); Dryness and inflammation of mouth: 12 (11.1%); and Enlargement of lymph nodes in the submandibular region: 1 (0.9%).

significant co-morbidities when only two days later, he was diagnosed SARS-CoV-2 positive. In another recent meta-analysis of valid questionnaire study by Chen et al[30] including a total of 108 participants with 52 males and 55 females, 47.2% of the participants reported amblygeustia while 46.3% reported xerostomia, 11.1% of the patients reported inflammation of mouth and enlargement of lymph nodes in the submandibular region was reported in 0.9% of the patients. (Table 1) In a similarly analysis by Abalo-Lojo et al[31] of 131 SARS-CoV-2 active patients, 55% reported both olfactory and gustatory dysfunction while 3.8% only olfactory and 1.5% only gustatory dysfunction. Also, 39.7% of the patients reported none of above symptoms while the other common COVID-19-associated symptoms included dry cough, asthenia, myalgia, headache, diarrhoea, fever (>38˚c), anorexia, dyspnea, tightness in the chest, nausea, abdominal pain and vomiting. Another notable finding in the said study was that 13.9% of the cases had developed symptoms on day one, 70.9% on day 3 while the remaining 15.2% after day 4 of the onset of infection. In the same study, 13 patients were found positive for the oro-pharyngeal swab nucleic acid detection while 4 of them were, also, tested positive for pure salivary gland secretion (i.e. saliva) highlighting the role oropharyngeal secretions and saliva might have in an early detection as well as being a potential source of infection transmission in confirmed SARS-CoV-2 infection. (Table 2)

A validated controlled trial conducted in the University of Pennsylvania on 60 confirmed SARS-CoV-2 infected patients by Moein et al[32], 98% of the patients reported olfactory dysfunction including 58%, complete anosmia, 33%, severe microsmia, 27%, moderate microsmia while 8% of the patients reported mild microsmia. Furthermore, 23% of the positive patients reported gustatory dysfunction as an early symptom of SARS-CoV-2 infection. (Table 2) In another larger-scale research from Europe by Lechien et al[17] on 417 confirmed SARS-CoV-2 infected patients, 85.6% and 88.0% of patients reported olfactory and gustatory dysfunction respectively. Furthermore, olfactory dysfunction appeared before other symptoms in 11.8% of the cases while females were found to be affected more as compared to males for olfactory and gustatory dysfunction. Also, phantosmia and parosmia were reported in 12.6% and 32.4% of the patients respectively while among the patients who did not complain of nasal stuffiness and rhinorrhoea, the rates of anosmia and hyposmia reported were found to be 66.2% and 13.5% respectively. (Table 2)

Interestingly, in a web based questionnaire study on 140 quarantined patients, 38.3% and 32.8% of the patients reported impaired sense of smell and taste respectively as their initial symptoms while a total of 25.8% of the patients stated olfactory and gustatory dysfunction in the absence of any other symptoms. Moreover, more than 50% of the patients, also, reported xerostomia and dysgeusia both as the prominent oral manifestations of SARS-CoV-2 infection. In addition to the above mentioned findings, 22 patients, also, reported paresthesia in relation to the tongue while 9 patients reported of having plaque-like changes in tongue. Furthermore, 10 patients had, also, reported swelling in the oral cavity with 4 patients having palatal swelling, the other 4 patients having swelling in relation to the tongue and 2 of them having swelling in relation to the gingival tissues.[33] The findings of xerostomia and dysgeusia in confirmed cases of SARS-CoV-2 infection can be explained by the fact that olfactory and gustatory senses are necessary for stimulation of saliva secretion. Thus, any grade of olfactory and gustatory dysfunction leads to impairment of neurological stimulation that might have led to xerostomia and secondary, dysgeusia in the affected patients.[34,35]

Melley et al[36], also, in their report of a 59 years old female patient, suggested hypogeusia and hyposmia as the early symptoms of infection in the patient with hyposmia later turning-out to complete anosmia with the passage of time. Similarly, in a literature of European Journal of Case Reports in Internal Medicine, two aged patients including an 85 years old male and 80 years old female patient, reported a history of sudden anosmia and fatigue in the asymptomatic stage of infection with a concomitant history of ageusia actually preceding complete anosmia in the patients.[37] A letter to

Table 2: Olfactory and gustatory dysfunction in SARS-CoV-2 infection

First Author/ Reference	Patient's Mean Age/ Gender Distribution/ Sample size	Any others Co-morbidities/Severity of COVID-19	Olfactory and gustatory dysfunction. Clinical outcomes/Early onset of olfactory dysfunction (before other symptoms or, hospitalization	COVID-19-associated other symptoms
Abalo-Lojo et al[31]	Mean age 50±4 years; Males 42.6%; Females 57.4%. Sample size: 131	Not mentioned. Not mentioned.	55% reported both olfactory and gustatory dysfunction; 3.8% only olfactory dysfunction; 1.5% only gustatory dysfunction; 39.7% reported none of above. On day one, 13.9% cases reported with symptoms, on day 3, 70.9% while the remaining 15.2% after day 4.	Dry cough, asthenia, myalgia, headache, diarrhoea, odynophagia, fever (>38°c), anorexia, dyspnea, expectoration, chest tightness, dizziness, nausea, abdominal pain, vomiting and conjunctivitis.
Moein et al[32]	Mean age 46.55±12.17 years; Males 66.7%; Females 33.3%. Sample size: 60	Diabetes with hypertension. Mild to severe.	98% reported olfactory dysfunction including 58% complete anosmia, 33% severe microsmia, 27% moderate microsmia while 8% mild microsmia; 23% reported gustatory dysfunction.	Fever (n = 46, 77%), cough (n = 35, 58%), shortness of breath (n = 31, 52%), headache (n = 22, 37%), myalgia (n = 5, 8%), increased sweating (n = 2, 3%), chills (n = 2, 3%), anorexia (n = 2, 3%), stomach-ache (n = 1, 2%) and tinnitus (n = 1, 2%).
Lechien et al[17]	Mean age 36.9±11.4 years; Males 37%; Females 63%. Sample size: 417	Allergic rhinitis (20%), asthma, hypertension, hypothyroidism. Mild to moderate.	85.6% and 88.0% of patients reported olfactory and gustatory dysfunction respectively. Olfactory dysfunction appeared before other symptoms in 11.8% of cases. Females were more affected as compared to males for olfactory and gustatory dysfunction.	Cough, myalgia, loss of appetite, diarrhoea, fever, headache and asthenia.
Klopfenstein et al[42]	Mean age 47±16 years; Males 33%; Females 67%. Sample size: 114	Hypertension, cardiovascular disease, asthma. Not mentioned.	47% reported olfactory dysfunction (anosmia) while 85% reported dysgeusia.	Fatigue (93%, n = 50), cough (87%, n = 47), headache (82%, n = 44), fever (74%, n = 40), myalgia (74%, n = 40), arthralgia (72%, n = 39) and diarrhoea (52%, n = 28).
Beltrán-Corbellini et al[41]	Mean age 61.6±17.4 years; Males 60.8%; Females 39.2%. Sample size: 79	--	31.65% reported olfactory dysfunction including 45.7% complete anosmia, 29% hyposmia and 6.5% dysosmia among 31 COVID-19 patients with olfactory and gustatory dysfunction; 35.44% reported gustatory dysfunction including 45.2% complete ageusia, 22.6% hypogeusia and 25.8% dysgeusia among 31 COVID-19 patients with olfactory and gustatory dysfunction. Early onset disease was seen in 35.5% of the 31 COVID- 19 patients presenting with olfactory and gustatory dysfunction.	Not mentioned.
Giacomelli et al[8]	Median age 60 years; Males 67.8%; Females 32.2%. Sample size: 59	--	11.9% reported complete anosmia while an equal number of patients, 11.9%, reported hyposmia; 13.6% reported ageusia while 15.3% dysgeusia. 20.3% reported olfactory dysfunction while 91% gustatory dysfunction as early onset disease symptoms.	Fever, cough, dyspnoea, sore throat, arthralgia, coryza, headache, asthenia and abdominal symptoms.

editor in (Spain), also, suggested similar finding that anosmia persisted for more than two week in a 40 years old female patient and was more prominent than other clinical symptoms associated with SARS-CoV-2 infection.[38] *Walker* et al[39], in their study using google trends in 8 different countries, hypothesized that increase in searches for anosmia and onset of COVID-19 infection could be correlated with a surge in the cases reported for anosmia in the current pandemic. Evidence, also, suggests that isolated anosmia could be one of the initial symptoms of SARS-CoV-2 infection without manifestation of other SARS-CoV-2-related symptoms.[40]

In another questionnaire-*based study* in Spain *by* Beltrán-Corbellini et al[41], 31.65% of the patients reported olfactory dysfunction including 45.7%, complete anosmia, 29%, hyposmia and 6.5%, dysosmia among the 31 COVID-19 patients with olfactory and gustatory dysfunction while 35.44% patients reported gustatory dysfunction including 45.2%, complete ageusia, 22.6%, hypogeusia and 25.8%, dysgeusia among the patients included in the study. Furthermore, early onset disease was seen in 35.5% of the patients presenting with olfactory and gustatory dysfunction. (Table 2) The numbers of patients affected with olfactory and gustatory dysfunction, though, were found to be even more in another retrospective analysis done by Klopfenstein et al[42] in France who reviewed 114 medical files of confirmed COVID-19 patients and reported olfactory dysfunction (anosmia) in 47% of the patients while 85% of the patients reported with dysgeusia. (Table 2) (For full information on olfactory and gustatory dysfunction in SARS-CoV-2 infection, see Table 2)

A remarkable finding associated with SARS virus infection in the past, too, was that most of the patients presented anosmia as an early onset symptom of the reported viral infection.[43] Infections of influenza and para-influenza viruses, rhinoviruses and other endemic corona viruses including common cold and flu viruses have all been associated with a characteristic olfactory dysfunction in the past.[44] Recent anecdotal and scientific reports have, also, provided evidence that COVID-19-associated chemosensory impairment is not limited only to olfactory but a gustatory dysfunction as well in addition to *chemesthesis*.[45]

While the final drafting of this literature review, we came across a published article in JAMA Dermatology that correlated viral-induced exanthems along with skin rashes as a confirmed diagnosis of SARS-CoV-2 infection. Out of the 21 confirmed SARS-CoV-2 patients in an age range of 40-69 years in the said study conducted by Jimenez-Cauhe *et al*[46], evidence of skin rashes was reported in most of the patients while 6 had developed viral exanthems with a data of 6 patients with oral cavity rashes. The said lesions were, further, classed as being macular in 1 case to petechiae in 2 cases and macules with petechiae in 3 of the cases reported. (Table 1) Oral ulceration and erosions in confirmed SARS-CoV-2 cases can be explained by the fact that the named virus uses enzyme ACE-2 to facilitate its entry into the specific host cells which might result in a direct vascular and mucosal damage seen. Martín Carreras-Presas et al[23] have stated that SARS-CoV-2 patients had pain in their tongue which can be explained by the presence of high expression of angiotensin-converting enzyme-2 (ACE-2) on tongue as compared to the other sites in the oral cavity including buccal mucosa and gingival mucosa.

Not to forget, all the recent anecdotal data and research is based on a limited sample size and some case reports published are merely based on suspected COVID-19 cases without a confirmed laboratory diagnosis. There is always a probability of oral symptoms arising due to the combined effect of psychological change in patients due to the stress and anxiety related to the virus, a lack of proper oral hygiene, an imbalance in the microbiota as well as due to the drugs being used by the patient due to a concomitant co-morbidity or, immunomodulatory drugs to prevent the infection that might have triggered the oral manifestations. Furthermore, evidence has, also, suggested that olfactory dysfunction in SARS-CoV-2 patients results in anosmia/hyposmia which can be an initial symptom before the actual onset of other significant COVID-19-related symptoms. Also, olfactory dysfunction can be seen alone or, in associated with

gustatory dysfunction and vice versa. It is very unlikely that in millions of COVID-19 patients seen so far, evidence precisely on oral manifestations is still limited which might be due to a lack of proper facilities to rule-out the oral findings present or, due to a lack of effective screening with saliva and other oral mucosal secretions being potential sources of infection and carriers of the virus in patients suffering from this deadly corona virus disease.[47]

Conclusion

In the limited number of studies available to date, COVID-19 disease has been reported to be associated with different types of oral manifestations. In this context, during the pandemic, the possibility of COVID-19 disease should be carefully evaluated, particularly, in patients presenting with characteristic oral findings reported. On the other hand, it should be kept in mind that the disease may, also, show the oral findings related to viral infections, in general, with or, without a prodrome. A timely and accurate identification of the relevant oral manifestations, thus, may play a key role in the early diagnosis and management of this highly infectious disease. Data from more research work, however, is always mandated to know further this disease process and its pathogenesis and the clinical implications, the oral manifestations in this disease can have as initial symptoms of SARS-CoV-2 infection. An in-depth analysis of the lesions that surface on the oral mucosa as well as evidence-based study on the histopathology of the said lesions is, also, required to further confirm the role of saliva and mucosal exudates and infected secretions in the spread of this deadly infection. It is but obvious that more research are needed to understand the exact relationship between COVID-19 disease and the associated oral manifestations attributed to it.

Declarations

The authors declare that they have no conflicts of interest, that the work has been approved by the ethics committee responsible in the workplace, and do not declare means of financing of the work carried out.

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RESUMEN

La enfermedad del corona virus 2 del síndrome respiratorio agudo severo (virus SARS-CoV-2) apareció por primera vez en diciembre de 2019 en Wuhan, China, y desde entonces se ha extendido rápidamente por todo el mundo. Desde entonces, el brote de esta grave enfermedad viral se ha convertido en una amenaza global para la humanidad. El diagnóstico precoz y el aislamiento son las medidas más importantes necesarias para prevenir su propagación. La evidencia anecdótica reciente ha sugerido manifestaciones orales con o sin deterioro olfativo y gustativo en asociación con la enfermedad por coronavirus (COVID-19). La enzima convertidora de angiotensina-2 (ECA-2) se expresa en la mucosa oral en grandes cantidades y, por tanto, puede contribuir a las primeras manifestaciones de esta enfermedad viral mortal. Las manifestaciones bucales de la enfermedad por coronavirus pueden presentarse en forma de lesiones ulcerativas irregulares en relación con diferentes partes de la cavidad oral y, en particular, en relación con la mucosa adherida en la región del paladar duro, así como inflamación y posterior atrofia de las diversas papilas de la lengua. La disfunción olfativa y gustativa asociada también puede conducir a una pérdida parcial y / o incluso completa de la capacidad para oler y saborear en las primeras etapas del inicio de la enfermedad. La evidencia también ha sugerido la presencia de ácido nucleico del SARS-CoV-2 en la saliva humana, lo que la convierte en portadora de la enfermedad viral infecciosa y ayuda en su diagnóstico. Hemos buscado sistemáticamente la base de datos médica para el mismo y hemos revisado toda la literatura disponible hasta el 29 de junio de 2020.

The Quality of Life impaction by Tinnitus Comprehension

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ABSTRACT

Tinnitus is the sensation of sound in the absence of any external source, and the aim is to assess the impaction of tinnitus on QoL. 25-tinnitus sufferers were enrolled with a wide range of hearing loss thresholds (HLT) and tinnitus severity status. Tinnitus severity, anxiety and depression were assessed using tinnitus handicap inventory (THI), tinnitus functional index (TFI), and the hospital anxiety and depression scale (HADS), respectively. Pure tone air conduction audiometry was performed. The impaction of tinnitus perception on QoL was found higher in suffering group. The anxiety and depression scale figured in 40%, and 60%, respectively. The handed use was 20 rights handed and 5 left-handed. Bilateral tinnitus is experiencing in 76%. The HL occurred in 17(68%) of tinnitus patients. The description of tinnitus sound as whistling (40%), hissing (24%), pulsating (16%), ringing (8%), and high pitch noises (12%). Regarding THI questionnaire, tinnitus subjects are divided to 60% (mild), 30% (moderate), and 10% (severe). While TFI questionnaire, 50% showed a (mild), 25% (moderate), and 25% showed (severe). We postulated a strong significant positive association between HADS and tinnitus severity: THI (P=0.000) and TFI (P= 0.001). Those data revealed that tinnitus perception has negative impacts on QoL, and the severity may be altered by laterality.

Keywords: Tinnitus; THI; HLT; HADS; TFI; QoL

Introduction

Tinnitus is the sensation of sound in the absence of any external source[1]. The prevalence was 10-15% of the adult[1]. It is mostly subjective, but only described by the subjects, sometimes have serious psychological impacts on the person[2]. Several tinnitus questionnaires made up as Tinnitus Handicap Inventory (THI) (asses emotional, functional and catastrophic subscales)[3] and the Tinnitus Functional Index (TFI) (assess awareness, coping, concentration, sleeping, hearing, relaxation, social activity and anxiety and depression)[4], to investigate the influence of tinnitus on emotional, functional, hearing, anxiety and depression. The tinnitus prevalence increased with increasing age[5].

As persons response differently to different symptoms and disorders, this study aims to assess the impact of tinnitus perception on QoL of tinnitus sufferers.

Material and Methods

Study design and setting

This work conducted in National Center for Audiology and Speech as prospective observational study at period from 2nd of June to 18th of December 2019.

Participants

Many inclusion and exclusion criteria were set in this study. Inclusion criteria were as following: age between 30-70 years old, subjective tinnitus for at least 3 months, and no conductive HL. 25-tinnitus sufferers were included with a wide range of HLT and TSS.

Audiology examination

Pure tone air conduction audiometry was performed to assess the hearing level. Audiograms were measured with a calibrated diagnostic audiometer. The tones were presented at seven frequencies (0.5, 1, 2, 3, 4, 6, 8 kHz), and at different intensities, ranged from (-10 to 120 dBHL).

Behavior assessment

Handed was assessed via utilizing Edinburgh Handedness Inventory (EHI)[6]. Beside that, anxiety and depression were screened for all persons by HADS[6].

Tinnitus scoring

In order to assess the effect of tinnitus on QoL, the tinnitus group was asked to complete two questionnaires (THI and TFI).

Statistical tools

The SPSS software version 24 (Chicago, US) was used for all statistical analysis. The degree of HL (%), and the presence of tinnitus, were determined separately for each ear and compared between ears and groups by independent sample t- test. Descriptive data were summarized using means and standard deviations for continuous data and percentages for categorical data. P-value <0.05 was deemed significant.

Results

This study included 25 patients: 15(60%) males, and 10(40%) females. The age range of tinnitus participants was from 35 to 70 years olds. The mean±SD age of patients was 55±23 years. The anxiety and depression scale figured in 40%, and 60%, respectively. The handed use was 20 rights handed and 5 left-handed. Bilateral tinnitus is experiencing in 76%. The hearing loss occurred in 17(68%) tinnitus patients. 10% of persons could cope with their tinnitus. The description of tinnitus sound as whistling (40%), hissing (24%), pulsating (16%), ringing (8%), and high pitch noises (12%), as showed in table 1.

The pure tone audiometry was performed and for each ear is shown in figure 1(A, B, C). The left ear audiograms recorded higher hearing loss thresholds than the right ear at 3, 4, 6 and 8 kHz, with no significant level (P ≥ 0.05).

In addition, there was no significant different observed of the HL level between both genders, handed, anxiety and depression, tinnitus-severity, and laterality (sided) (bilateral and unilateral). Whereas there was a strong significant difference between normal and HL persons among hearing level (P<0.000), shown in table 2.

The overall results of THI and TFI are figured in table 3. Regarding THI questionnaire, tinnitus subjects are divided to 60% (mild), 30% (moderate), and 10% (severe). While TFI questionnaire, 50% showed a (mild), 25% (moderate), and 25% showed (severe).

We postulated a strong significant positive association between HADS and tinnitus severity: THI (P=0.000) and TFI (P= 0.001), as showed in figure 2.

Table 1. The characteristics of tinnitus participants (n=25).

Variables		No.	%
Gender	Male	15	60
	Female	10	40
Handed use	Rt	20	80
	Lt	5	20
Anxiety	Yes	10	40
	No	15	60
Depression	Yes	15	60
	No	10	40
Hearing level	Normal	8	32
	Loss	17	68
Severity of tinnitus	Copy	10	40
	Suffer	15	60
Sided	Unilateral	6	24
	Bilateral	19	76
Features of tinnitus	Whistling	10	40
	Hissing	6	24
	Pulsating	4	16
	Ringing	2	8
	High pitch noises	3	12

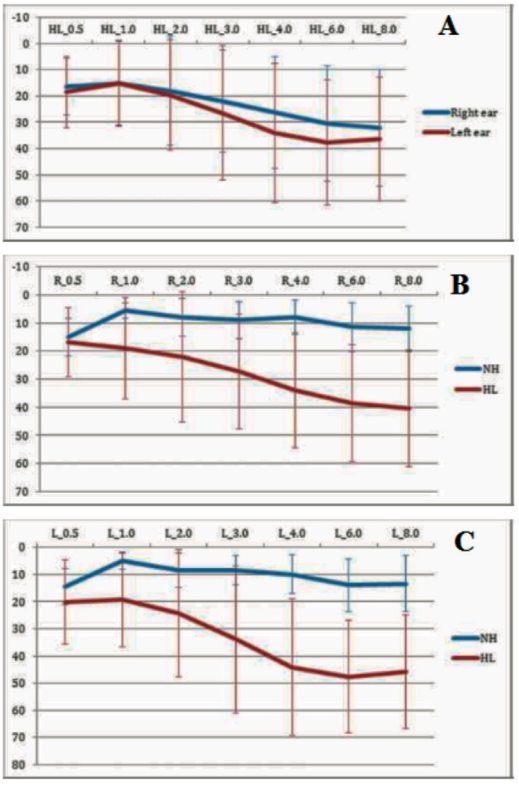
Table 2: The effect of different variables on hearing acuity.

Variables		HLT mean±SD (t-test)	P value
Gender	Male	49±20	0.3
	Female	41±25	
Handed use	Rt	42±20	0.09
	Lt	58±19	
Anxiety and Depression	Yes	50±18	0.5
	No	51±20	
Hearing level	Normal	67±3	0.000
	Loss	25±7	
Severity of tinnitus	Copy	48±19	0.9
	Suffer	48±21	
Sided	Unilateral	51±22	0.5
	Bilateral	49±26	

Table 3: The impact of tinnitus perception results using THI and TFI.

Questionnaire	Scores	%
THI	Mild	60
	Moderate	30
	Severe	10
TFI	Mild	50
	Moderate	25
	Severe	25

Figure 1. Normal hearing was defined as pure tone hearing thresholds of 20 dB or better at these frequencies, and hearing loss was defined as a hearing threshold more than 25 dB at any frequency.

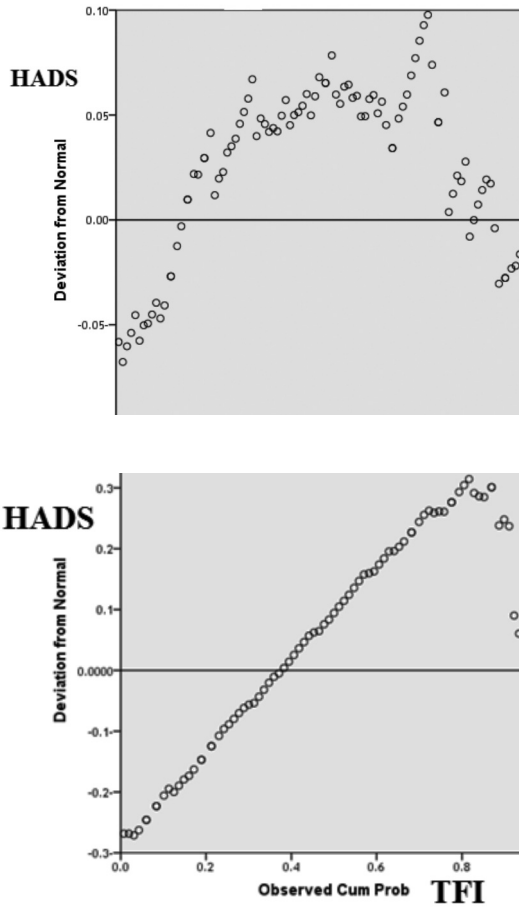


A: Pure tone audiometry, B: Rt ear audiograms, C: Lt ear audiograms.

Discussion

The prevalence of tinnitus in man more than women that is consistence with other[7]. The connection between sex and tinnitus severity was observed variables as some researchers found women showed higher scores comparing to male[8], while others have shown the opposite[5, 9], or other recorded no correlation[10]. Here, there was no significant difference between males and females in terms of HL and tinnitus severity was assessed.

Figure 2. Correlation between HADS, A: THI scores, and B: TFI.



Different studies concluded that there is no correlation between severity and age[2, 10]; however, Hiller and Goebel[11] found there is a positive correlation between severity and age.

The association between hearing impairments and loneliness was identified, which found that the incidence of loneliness is significantly higher in hearing impairment sampling comparing to normal[12, 13].

In this study, we found nearly two-third of the tinnitus participants had some degree of hearing loss, while one-third had normal hearing that is nearly consistent with a large epidemiology study[14].

There were no significant differences were recorded in the THI and TFI scores between tinnitus participants with normal hearing and tinnitus participants with hearing loss, which has been found as well in these previous studies[2, 14-16].

The laterality was not found to play a significant role severity in a study conducted by Alsanosi (overall THI score)[7]. Here, also did not find a significant difference in the THI score between unilateral and bilateral. However, unilateral tinnitus showed significant higher negative impactions than bilateral.

In conclusion, we demonstrated the negative impacts of tinnitus perception on QoL. The ageing factor was affected the hearing acuity of tinnitus population. Also, tinnitus laterality seems to play a factor on severity.

Declarations

The authors declare that they have no conflicts of interest, that the work has been approved by the ethics committee responsible in the workplace, and do not declare means of financing of the work carried out.

Resumen

El tinnitus es la sensación de sonido en ausencia de cualquier fuente externa. Nuestro objetivo fue evaluar la repercusión del tinnitus en la calidad de vida. Se inscribieron 25 pacientes con tinnitus con una amplia gama de umbrales de pérdida auditiva (HLT) y estado de gravedad de tinnitus. La gravedad, la ansiedad y la depresión del tinnitus se evaluaron mediante el inventario de discapacidades por tinnitus (THI), el índice funcional de tinnitus (TFI) y la escala de ansiedad y depresión hospitalaria (HADS), respectivamente. Se realizó una audiometría de conducción aérea de tono puro. El impacto de la percepción del tinnitus en la calidad de vida se encontró más alto en el grupo de sufrimiento. La escala de ansiedad y depresión figuraba en 40% y 60%, respectivamente. El uso de la mano fue de 20 diestros y 5 zurdos. El tinnitus bilateral se está experimentando en el 76%. El LH se presentó en 17 (68%) de los pacientes con tinnitus. La descripción del sonido del tinnitus como silbido (40%), siseo (24%), pulsante (16%), timbre (8%) y ruidos de tono alto (12%). Con respecto al cuestionario THI, los sujetos con tinnitus se dividen en 60% (leve), 30% (moderado) y 10% (grave). Mientras que el cuestionario TFI, el 50% mostró un (leve), el 25% (moderado) y el 25% mostró (severo). Postulamos una fuerte asociación positiva significativa entre HADS y la gravedad del tinnitus: THI (P = 0,000) y TFI (P = 0,001). Esos datos revelaron que la percepción del tinnitus tiene impactos negativos en la calidad de vida mientras que la gravedad puede verse alterada por la lateralidad.

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RESUMEN

El tinnitus es la sensación de sonido en ausencia de cualquier fuente externa. Nuestro objetivo fue evaluar la repercusión del tinnitus en la calidad de vida. Se inscribieron 25 pacientes con tinnitus con una amplia gama de umbrales de pérdida auditiva (HLT) y estado de gravedad de tinnitus. La gravedad, la ansiedad y la depresión del tinnitus se evaluaron mediante el inventario de discapacidades por tinnitus (THI), el índice funcional de tinnitus (TFI) y la escala de ansiedad y depresión hospitalaria (HADS), respectivamente. Se realizó una audiometría de conducción aérea de tono puro. El impacto de la percepción del tinnitus en la calidad de vida se encontró más alto en el grupo de sufrimiento. La escala de ansiedad y depresión figuraba en 40% y 60%, respectivamente. El uso de la mano fue de 20 diestros y 5 zurdos. El tinnitus bilateral se está experimentando en el 76%. El LH se presentó en 17 (68%) de los pacientes con tinnitus. La descripción del sonido del tinnitus como silbido (40%), siseo (24%), pulsante (16%), timbre (8%) y ruidos de tono alto (12%). Con respecto al cuestionario THI, los sujetos con tinnitus se dividen en 60% (leve), 30% (moderado) y 10% (grave). Mientras que el cuestionario TFI, el 50% mostró un (leve), el 25% (moderado) y el 25% mostró (severo). Postulamos una fuerte asociación positiva significativa entre HADS y la gravedad del tinnitus: THI (P = 0,000) y TFI (P = 0,001). Esos datos revelaron que la percepción del tinnitus tiene impactos negativos en la calidad de vida mientras que la gravedad puede verse alterada por la lateralidad.

Novel risk factors of pulmonary hemorrhage complicating CT-guided lung biopsy in coaxial technique

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ABSTRACT

Objectives: To evaluate the frequency and severity of pulmonary parenchymal hemorrhage after coaxial transthoracic needle biopsy of the lung, according to procedural factors, not yet described in literature. The aim of this study was to determine whether the choice of the coaxial biopsy technology, patient positioning and the lesion dignity are three new variables influencing the risk of parenchymal hemorrhage after coaxial biopsies of the lung. **Methods:** Records from 117 patients who underwent transthoracic needle biopsies of the lung between January 2018 and April 2020 have been retrospectively reviewed. The primary outcome was pulmonary hemorrhage. A grading system has been used to classify pulmonary parenchymal hemorrhage: Grade 0 – Grade 3. Three novel patient, technique and lesion-related variables were evaluated as predictors of pulmonary hemorrhage: coaxial biopsy technology, patient positioning and lesion dignity. **Results:** Out of the 117 patients, 18 (15,4%) patients with cutting coaxial biopsy technology, versus 29 (24,8%) patients with full core coaxial technology showed significant hemorrhage on the post-biopsy control scans. (95% CI 0,06-0,33, p<0,0001). No significant difference in pulmonary hemorrhage between benign and malignant histological diagnosis (95% CI 0,84-4,44, p=0,1199) and prone or supine patient positioning (95% CI: 0,57-2,57, p= 0,6232) was found. **Conclusions:** The incidence and severity of pulmonary hemorrhage depends on the coaxial biopsy technology used; being higher in patients undergoing a biopsy with full-core technology and lower after the use of cutting technology. No significant correlation between parenchymal pulmonary hemorrhage and patient positioning or lesion dignity was established in this prognostic study.

Keywords: lung biopsy, pulmonary hemorrhage, coaxial biopsy system, cutting technology, full-core technology, risk factors

Abbreviations: TTLB: transthoracic lung biopsy; SIR: Society of Interventional Radiology; CT: computed tomography; OR: Odds Ratio; CI: 95% confidence interval; p: significance level p.

INTRODUCTION

Diagnostic lung biopsies using coaxial biopsy systems have become a standard procedure in most interventional radiology departments and are associated with a comparable diagnostic accuracy to other biopsy systems (1). Lower rates of pneumothoraxes and time reduction have been described with coaxial cutting systems (1).

After pneumothorax, pulmonary hemorrhage is the second most common complication of needle biopsy of the chest. (2, 3).

Previous studies have determined subsolid lesions as a risk factor for severe hemoptysis and higher-grade parenchymal hemorrhage (4, 5)Francine L</author><author>Madan, Rachna</author><author>Kumamaru, Kanako K</author><author>Hunsaker, Andetta R</author></authors></contributors><titles><title>Frequency and severity of pulmonary hemorrhage in patients undergoing percutaneous CT-guided transthoracic lung biopsy: single-institution experience of 1175 cases</title><secondary-title>Radiology</secondary-title></titles><periodical><full-title>Radiology</full-title></periodical><pages>287-296</pages><volume>279</volume><number>1</number><dates><year>2016</year></dates><isbn>0033-8419</isbn><urls></urls></record></Cite><Cite><Author>Song</Author><Year>2013</Year><RecNum>7</

RecNum><record><rec-number>7</rec-number><foreign-keys><key app="EN" db-id="rwwzpdtfo2pxx4epsrv52rebv99zszx9vade" timestamp="1588855798">7</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Song, Yong Sub</author><author>Park, Chang Min</author><author>Park, Kyung Woo</author><author>Kim, Kwang Gi</author><author>Lee, Hyun-Ju</author><author>Shim, Mi-Suk</author><author>Goo, Jin Mo</author></authors></contributors><titles><title>Does antiplatelet therapy increase the risk of hemoptysis during percutaneous transthoracic needle biopsy of a pulmonary lesion?</title><secondary-title>American Journal of Roentgenology</secondary-title></titles><periodical><full-title>American Journal of Roentgenology</full-title></periodical><pages>1014-1019</pages><volume>200</volume><number>5</number><dates><year>2013</year></dates><isbn>0361-803X</isbn><urls></urls></record></Cite></EndNote>.

Yeow et al. (2) have stated that the needle size, number of biopsies, pleural puncture site position after needle biopsy, location of the lung lesions, patient's age, and emphysema were not associated with an increased risk of parenchymal hemorrhage. Lesion size, lesion depth and pleural effusion have been described as being significantly associated with pulmonary hemorrhage (2).

Pneumothoraxes and parenchymal hemorrhage have furthermore been described to significantly correlate with lesion sizes ≤ 2cm and lesion depth (2). Lesion depth ≥ 2,1 cm correlate to an elevated bleeding risk. Lesion size < 4 cm is strongly correlated with higher occurrence of perifocal hemorrhage (3).

Considering these variables, the aim of this study was to determine whether the coaxial biopsy technology, patient positioning and lesion dignity are three new risk factors of parenchymal hemorrhage after coaxial biopsies of the lung. **(Figures 1-3)**

Regarding pneumothorax, the most common complication after transthoracic lung biopsies, several studies correlated the incidence and severity with patient positioning (6-8). Other studies correlated inflammatory lesions with higher rates of systemic air embolism (9-11). The aim of our study was to correlate these variables as potential risk factors for pulmonary parenchymal hemorrhage.

Figure 1: Coaxial biopsy system with cutting technology (Archieve®).

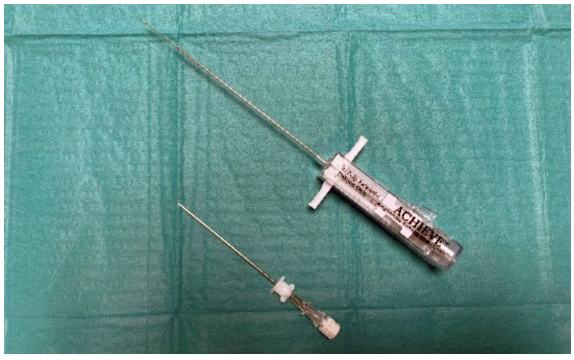


Figure 2: Coaxial biopsy system with full-core technology (CorVocet®).

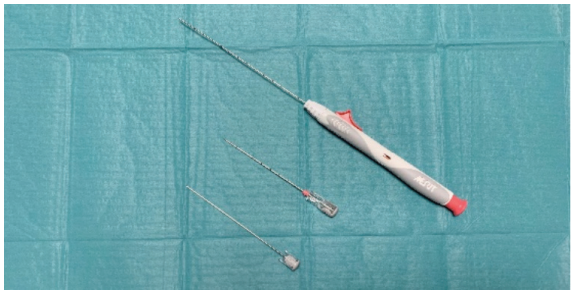
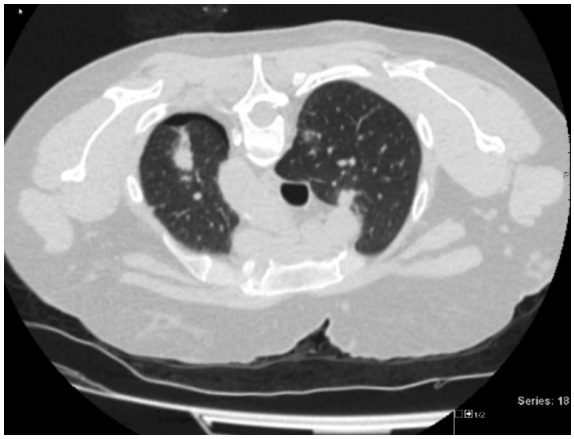


Figure 3: Prone positioning of a patient post-biopsy with a small pneumothorax and no relevant parenchymal hemorrhage (grade 1).



MATERIAL AND METHODS:

Data Collection

Three radiology physicians with five, six and eight years of experience respectively retrospectively analyzed acquired CT images during the biopsy procedure. The correlating pathological diagnosis of the biopsy specimens, as well as the patient history were acquired through the clinical data collecting system.

Pulmonary hemorrhage was classified according to a grading scheme, ranging from 0 to 3. The presence of parenchymal hemorrhage, consisting of the search for ground-glass opacity and more confluent hemorrhages after biopsy was assessed for each procedure.

The grading scheme was developed and modified according to existing literature (2, 4)Ryan</author><author>Dunne, Ruth M</author><author>Trotman-Dickenson, Beatrice</author><author>Jacobson, Francine L</author><author>Madan, Rachna</author><author>Kumamaru, Kanako K</author><author>Hunsaker, Andetta R</author></authors></contributors><titles><title>Frequency and severity of pulmonary hemorrhage in patients undergoing percutaneous CT-guided transthoracic lung biopsy: single-institution experience of 1175 cases</title><secondary-title>Radiology</secondary-title></titles><periodical><full-title>Radiology</full-title></periodical><pages>287-296</pages><volume>279</volume><number>1</number><dates><year>2016</year></dates><isbn>0033-8419</isbn><urls></urls></record></Cite></EndNote>.

Grade 0 was defined as no pulmonary hemorrhage, grade 1 as hemorrhage not overpassing the needle tract in length or width by more than 2,5 cm, grade 2 as hemorrhage more than 2,5 cm in width or length along the needle tract, grade 3 as lobar hemorrhage or greater, including hemothorax. **(Figures 4-5)**

A biopsy was registered as successful if a sufficient quantity of tissue out of the target lesion was sampled by the biopsy procedure and only the diagnostic specimen were included, as this study did not evaluate the diagnostic accuracy.

Three patient, technique and lesion-related variables were evaluated as predictors of pulmonary hemorrhage. The patient-related variable consisted of patient positioning. The technique-related variable of the type of the coaxial system and the lesion-related variable of the lesion dignity.

Figure 4: Grade 0 parenchymal hemorrhage (top left), grade 1 parenchymal hemorrhage (top right), grade 2 parenchymal hemorrhage (bottom).

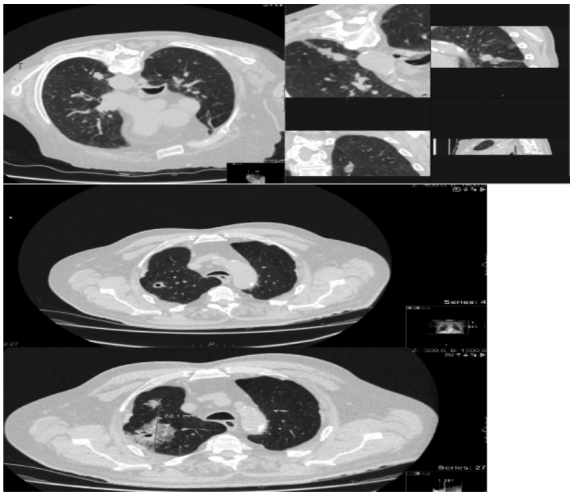
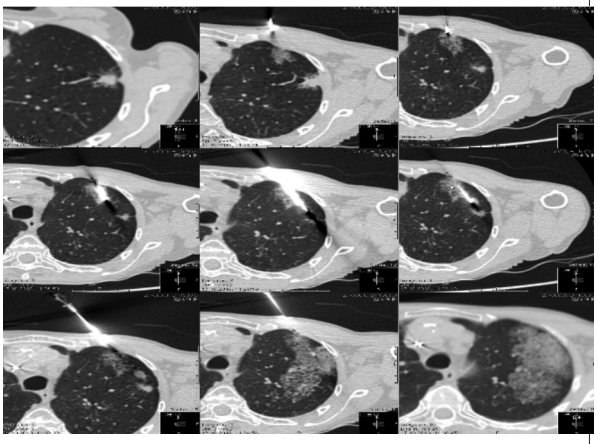


Figure 5: Grade 3 parenchymal hemorrhage.



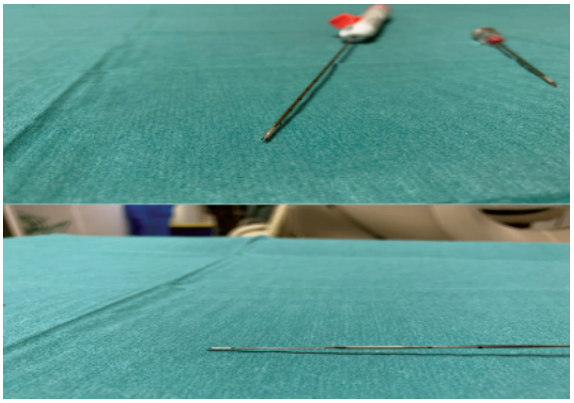
Patients and biopsy technique

A retrospective analysis of 117 consecutive lung biopsy procedures with different coaxial cutting systems between January 2018 and April 2020, involving patients with a documented pulmonary nodule or mass lesion on previous CT scans has been performed.

The study population included 80 males (68,4 %) and 37 females (31,6 %) aged 28-89

years (mean age 67,6 years). Image-guided procedures with two different co-axial cutting systems (Temno®, Merit Medical and Achieve®, Merit Medical) have been performed in 75 (64,1%) patients. **(Figure 6)**

Figure 6: Coaxial biopsy system with full-core technology needle tip (CorVocet®, top) and with cutting technology needle tip (Temno®, bottom).



The study includes 42 (35,9%) patients, who underwent a procedure with a co-axial cutting system with full core technology (CorVocet®, Merit Medical). **(Table 1)**

Table 1: Patient, tumor, and biopsy system-related characteristics.

Distribution of Variable Characteristics	Number/Prevalence
Total	n = 117
Sex	
Male	n = 80 (68.4%)
Female	n = 7 (31.6%)
Coaxial Biopsy Technology	
Cutting Technology	n =75 (64.1%)
Full-Core Technology	n = 42 (35.9%)
Lesion Dignity	
Malignant	n = 80 (68.4%)
Benign	n = 37 (31.6%)
Patient Positioning	
Prone/lateral	n = 69 (59%)
Supine	n = 48 (41%)

Only patients who underwent a biopsy with a 18G biopsy needle were included in this study.

Pathological analysis of the specimens

Detailed histological information on the subtype of the neoplasms and the differentiation into benign or malignant lesions were included in the pathology assessment, which was performed routinely in our pathology institute.

In the case, that sufficient material had been obtained for a histopathological analysis to yield a diagnosis of a malignant or benign lesion, the biopsy was defined as diagnostic.

Complications

We reported and classified all early complications during the biopsy procedure in the sense of immediate complications and complications after an observation time of two to four hours after the biopsy procedure using the international standardized and revised SIR (Society of Interventional Radiology) Classification System for Complications by Outcome to differentiate minor from major complications. In our present study we included patients with pulmonary hemorrhage on the interventional and post-interventional CT-scans.

On the other hand, for the registration of eventual other late complications, we reviewed the following hospital history in our electronic patient care software. Other complications, such as pneumothorax were not included in this study.

Statistical Analysis

Our three novel factors related to the patient, target lesion and biopsy procedure were recorded (patient positioning, coaxial biopsy technology and dignity of the lesion).

The classification of hemorrhage degree consisted of two categories: no or small hemorrhage (included degree 0 and 1) and significant hemorrhage (included degree 2 and 3) respectively.

These factors were evaluated in univariate analysis. Considering the statistical outcome of the described previous studies, that showed no correlation between patient age, sex, needle size, number of biopsies, pleural puncture site, position of the needle, location of the lung lesions, patient's age and emphy-

sema, no further univariate or multivariate analyses including these parameters have been performed (2).

We also considered that it is of limited interest and effectiveness to rank our three variables in subgroups for a multivariate statistical analysis, due to the lack of pre-biopsy diagnosis of a benign or a malignant lesion, so that an adoption of the coaxial biopsy technology is not possible in advance of the intervention. Furthermore, a selective patient positioning is only possible and adaptable in limited cases, due to physical patient restrictions.

These data were recorded in the biopsy data reports by the interventional radiologists and have been retrospectively controlled and evaluated for our retrospective study.

Results

Significant pulmonary hemorrhage, including grade 2 and 3 of our classification system occurred after 47 of the 117 lung biopsy procedures (40,2%). No (grade 0) and no significant hemorrhage (grade 1) occurred in 70 patients (59,8%). Four of the 117 TTLBs (3,4%) resulted in grade 3 hemorrhage, 43 (36,8%) in grade 2 hemorrhage, 39 (33,3%) in grade 1 hemorrhage, and 31 (26,5%) in grade 0 hemorrhage. **(Table 2)**

18 (15,4%) patients who underwent a procedure with cutting coaxial biopsy technology showed a significant parenchymal hemorrhage, whereas 29 (24,8%) patients with full core coaxial technology showed significant hemorrhage on the post-biopsy control scans, versus 57 (48,7%) and 13 (11,1%) patients without significant hemorrhage respectively. OR=0,1416 (CI: 0,0610-0,3285); p<0,0001.

36 (30,8%) patients with a malignant histological diagnosis showed significant pulmonary hemorrhage, versus 11 (9,4%) patients with a benign histological diagnosis on the post-biopsy specimen. 44 (37,6%) patients with a malignant process had no significant hemorrhage versus 26 (22,2%) patients with a benign diagnosis. OR=1,9339 (CI: 0,8422-4,4407); p=0,1199.

In the third evaluated category, 29 (24,8%) patients in prone or lateral position during the biopsy procedure showed significant post-biopsy pulmonary hemorrhage, versus 18 (15,4%) patients in supine position. No significant parenchymal hemorrhage was observed in 40 (34,1%) patients in prone/lateral position and 30 (25,7%) patients in supine position respectively. OR=1,2083 (CI: 0,5679-2,5708); p= 0,6232.

One patient in the category of grade 3 hemorrhage required bronchoscopy. The remaining three patients with grade 3 hemorrhage did not require additional interventions.

The registration of late complications in our electronic patient care software and on the imaging performed in the week after the

Table 2: Distribution of significant vs. no significant pulmonary hemorrhage.

Variable	Pulmonary hemorrhage				
n = 117 (Total number of patients)	**Developed**	**Not Developed**	**Odds Ratio**	**Confidence interval**	**p value**
Biopsy System					
Cutting system	18 (15.4%)	57 (48.7%)			
Full core	29 (24.8%)	13 (11.1%)	0.1416	0.0610-0.3285	<0.0001
Lesion Dignity					
Malignant	36 (30.8%)	44 (37.6%)			
Benign/inflammatory/infectious	11 (9.4%)	26 (22.2%)	19.339	0.8422-4.4407	0.1199
Patient Positioning					
Prone/Lateral	29 (24.8%)	40 (34.2%)			
Supine	18 (15.4%)	30 (25.6%)	12.083	0.5679-2.5708	0.6232

lung biopsy showed no worsening further parenchymal hemorrhage or major hemorrhage-related complication.

Discussion

Widely established protocols for a safe and successful lung biopsy with coaxial biopsy systems have been described (12). The choice between the different coaxial biopsy systems depends upon personal selection criteria, without a complete and exhaustive scientific-based availability of risk analysis. The rapidly evolving market of biopsy technologies offers a wide range of coaxial biopsy systems in particular.

Novel risk factors for pneumothoraxes, including patient positioning and needle paths through atelectasis have been determined (13-15).

However, considering the second most common complication after lung biopsies, notably parenchymal hemorrhage, none of our three studied criteria (dignity of the lesion, coaxial biopsy technology and patient positioning) has been paid closer attention to in literature.

The incidence of postprocedural pneumothorax in our study correlates very well with other studies (24%) (2, 3, 16).

Pulmonary hemorrhage was described as having a potential preventive effect on the development of pneumothorax through a sealing effect in the biopsy path (17). Other factors have been studied to reduce air leak after removal of the needle using blood-patches and injection of tissue adhesives through the needle tract (18-21).

Three novel risk factors of parenchymal pulmonary hemorrhage have been evaluated in patients following a coaxial lung biopsy and further studies with larger patient populations allowing an additional multivariate analysis are necessary to determine whether or not patient positioning and lesion dignity can be definitely excluded as a risk factor for pulmonary hemorrhage following percutaneous lung biopsies. However, the interest and consequences of such a study are limited, due to the fact that lesion dignity can only be conclusively evaluated after histological examination. Patient positioning may also be biased by the physical condition of the patients. The higher incidence and severity of pulmonary hemorrhage in lung biopsy, after the use of a coaxial technique with full core technology, could be explained by the more powerful and eventually more tissue damaging shot of these systems.

In conclusion, a statistically significant relation exists between the incidence, as well as the severity of pulmonary hemorrhage and the coaxial biopsy technology used. Coaxial biopsy techniques with full core technology seem to be more tissue damaging than conventional cutting systems. No significant correlation between parenchymal pulmonary hemorrhage and patient positioning or lesion dignity was established in this prognostic study.

Key points:

The evaluation of the frequency and severity of pulmonary parenchymal hemorrhage after coaxial transthoracic needle biopsy of the lung, according to three new procedural factors, not yet described in literature.

Analyzing patient, lesion, and biopsy system-related risk factors of pulmonary hemorrhage: lesion dignity, type of coaxial biopsy system and patient positioning.

Safety comparison between coaxial biopsy system technologies: cutting needle versus full-core technology.

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RESUMEN

Objetivos: Evaluar la frecuencia y gravedad de la hemorragia parenquimatosa pulmonar tras la biopsia pulmonar con aguja transtorácica coaxial, según factores de procedimiento, aún no descritos en la literatura. El objetivo de este estudio fue determinar si la elección de la tecnología de biopsia coaxial, el posicionamiento del paciente y la dignidad de la lesión son tres nuevas variables que influyen en el riesgo de hemorragia parenquimatosa tras biopsias coaxiales de pulmón. **Métodos**: Se revisaron retrospectivamente los registros de 117 pacientes que se sometieron a biopsias con aguja transtorácica del pulmón entre enero de 2018 y abril de 2020. El resultado primario fue la hemorragia pulmonar. Se ha utilizado un sistema de clasificación para clasificar la hemorragia parenquimatosa pulmonar: Grado 0 - Grado 3. Se evaluaron tres variables novedosas relacionadas con el paciente, la técnica y la lesión como predictores de hemorragia pulmonar: tecnología de biopsia coaxial, posición del paciente y dignidad de la lesión. **Resultados**: De los 117 pacientes, 18 (15,4%) pacientes con tecnología de biopsia coaxial de corte, versus 29 (24,8%) pacientes con tecnología coaxial de núcleo completo mostraron hemorragia significativa en las exploraciones de control posteriores a la biopsia. (IC del 95% 0,06-0,33, p <0,0001). No hubo diferencias significativas en la hemorragia pulmonar entre el diagnóstico histológico benigno y maligno (IC 95% 0,84-4,44, p = 0,1199) y la posición del paciente en decúbito prono o supino (IC 95%: 0,57-2,57, p = 0,6232). **Conclusiones**: La incidencia y gravedad de la hemorragia pulmonar depende de la tecnología de biopsia coaxial utilizada; siendo mayor en pacientes sometidos a una biopsia con tecnología full-core y menor después del uso de tecnología de corte. En este estudio de pronóstico no se estableció una correlación significativa entre la hemorragia pulmonar parenquimatosa y la posición del paciente o la dignidad de la lesión.

Mental Disorders after Hospitalization for Covid 19

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SUMMARY

Introduction: The purpose of this study was to investigate possible mental disorders in patients who contracted Covid19 during the 2020 pandemic and were hospitalized in a Greek hospital - outside the intensive care unit - and their comparative evaluation with those who were admitted quarantine without the onset of severe symptomscovid19. Method: The study involved 348 adults from Greece, namely 166 patients who were discharged after hospitalization in a pandemic reference hospital, and 182 asymptomatic and unpatrolled individuals who were quarantined in a familiar environment during the event. pandemic. Results: People who were hospitalized in the country due to covid symptoms 19, present the period after their discharge mental disorders mainly depression and post-traumatic stress. Those who were placed in compulsory quarantine did not show similar symptoms. **Conclusions**: The nature and characteristics of covid 19 disease as well as simple hospitalization seem to create, among other things, post-traumatic stress disorder and depression that manifest and follow patients in the time period after their discharge. Symptoms of depression and feelings of intense anger also appear to manifest. These results show a part of the disorders and psychopathology of patients with covid19 after their treatment. The manifestation of these mental disorders seems to be related to the specific conditions of the pandemic disease, its extent, intensity, as well as its characteristics such as social isolation, mortality and contagion. The investigation as well as the timely and appropriate treatment of the context of mental disorders - especially post-traumatic stress and depression - should receive special attention and be the subject of broader research over time.
Keywords: mental disorders, hospitalization. Covid19

Introduction

Post Traumatic Stress Disorder (PTSD) is a stress disorder that can occur in a person who has had a dangerous traumatic experience, in which there has been actual or threatened death, serious injury, or threat to his or her own or others' physical integrity. This traumatic event is accompanied by intense fear, helplessness or horror. The disorder can affect survivors of rape, physical abuse, war, torture, natural disasters, car or air accident, hostage situation or death camp. Whatever the traumatic event, the person has lived through a period of intense fear, despair, and loss of control.

Among Vietnam veterans, 14% reported developing a severe form of PTSD and among survivors of an accident at work in 1988 at an oil rig in the North Sea where 75% of men died in the blast, the remaining 25% did not develop excluding. Very young and elderly people who suffer significant trauma seem to be particularly prone to post-traumatic stress, probably because young children do not have sufficiently developed defense mechanisms to cope, and the elderly because they may have less social support. An important aspect of the disorder is that not all people who witness the same event suffer from post-traumatic stress disorder. This leads us to conclude that there are factors that influence the genesis or not of the disorder.

Gender is an important element in post-traumatic stress disorder. Twice as many women as men suffer from the disorder. The personality of each person is an important factor, the attitude towards life, how each one interprets and evaluates the experiences and events of life in combination with the psychological problems that the person may face (depression, anxiety disorders). The support that the individual can receive from his environment, family or friend is a catalyst for the healing of the wound (Stephenson, 2001).

Post - traumatic stress disorder (PTSD)

Post-traumatic stress disorder (PTSD) was first described in World War I veterans as "bombing shock" and was originally described as "nervous shock", "traumatic neurosis" or "phobic neurosis". Symptoms included feelings of extreme hostility to others, intense and unwarranted outbursts of anger, and fixation on traumatic events. The specific name PTSD first appeared in the late 1970s and concerned the long-term effects of exposure to traumatic war events. Typical symptoms of the disorder include emotions of war veterans who seem to relive traumatic events and exhibit avoidance behaviors as well as physical symptoms. Today it is also used to convey a broader context of mental phenomena such as drug addiction, or immigration and hospital emergencies (Stephenson, 2001).

Post-traumatic stress is one of the most common and debilitating psychological consequences of a disaster. It refers to situations in which traumatic events are experienced outside the context of everyday life and which cause discomfort or despair. An important predictor of developing this disorder is the inability to react in combination with feelings of fear, physical arousal and a sense of helplessness (Armor, et al., 2011). People who develop PTSD show permanent changes in their brain (hypothalamus - pituitary gland - adrenal gland - amygdala) (Stephenson, 2001). An example that shows the strong impact of the catastrophic events of life is the case of the volcano of Saint Eleni, when a few months after its eruption in the nearby town of Othello there was an increase in deaths of 18.6%, an increase in diseases aggravated by stress 19.8% and twice the number of people seeking mental health services (Armor, et al., 2011).

The symptoms of Post Traumatic Stress are categorized into three categories. The first context includes reliving the traumatic experience, flashbacks, nightmares, and psychosomatic stress. The second set of symptoms includes persistent avoidance of thoughts, persons, or situations experienced as reminders of the traumatic experience, inability to retrieve information about the traumatic event or withdrawal from activities or specific individuals, and lack of plans for the future (Armor, et al., 2011). The third context includes symptoms of particular intensity such as sleep disturbances, irritability, hyperexcitability, difficulty concentrating, sudden reactions as well as physical symptoms (Gilbert et al., 2003).

The present study

The aim of this study was to investigate the manifestation of mental disorders in patients with covid 19 coronary after their discharge from hospital. Specifically, an attempt was made to investigate the presence of symptoms of post-traumatic stress, depression or other mental disorders that could be caused by the disease and the special conditions of treatment related to social isolation, the possibility of worsening and death, transmission, etc.

Specifically, the main goal of this research study was to detect the post-traumatic psychosocial issues of people who became ill and were treated by covid19 during the period from March to June 2020 in Greece.

A comparison was made between the group of patients who contracted coronary heart disease and were admitted to a hospital in any area of Greece and the individuals who were placed (as carriers of the disease) in mandatory quarantine.

Sample

The study involved 348 adults from Greece, namely 166 patients who were discharged after hospitalization in a pandemic reference hospital (77 men,89women), and 182 asymptomatic and unpatrolled individuals (109 men, 73 women) who were quarantined in a familiar environment during the pandemic. The mean age of the participants was 40.2 years with a standard deviation of 8.3 years. The conditions for the participation of the individuals in the study were: their hospitalization in a health unit, but not in an intensive care unit, or their stay in quarantine for a period of at least fourteen days. The desire of individuals to participate in the present study voluntarily and to have no previous history of any mental disorder. The people who participated in the study were informed about the anonymity and protection of their data as well as about its purpose.

Procedure

The research was carried out through the response of the participants to the research tools which were posted on the configured response platform of Google drive. The demographics of the participants were recorded for the research, such as: gender, age, place of residence, level of education, and previous medical history of mental illness or hospitalization in a clinic or hospital. The following research tools were used in the platform configured in the Google drive:

Psychopathology Scale (SCL-90) (Derogatis, 1977)

The Psychopathology Scale (SCL-90) concerns the recording of existing psychopathology. It consists of 90 questions, which describe psychological, behavioral, and physical objections in the base of 9 subscales: incarnation, obsessive compulsive, interpersonal sensitivity, depression, aggression, phobic anxiety, paranoid ideation, psychosis and various objections. The evaluation is performed according to a five-point Likert scale (0-1-2-3-4). In addition to the export index for each sub-scale, there are an additional 3 total indicators, which relate to the general symptom index, the total of positive symptoms and the positive symptom annoyance index respectively. The adjustment of the scale to the Greek population presented satisfactory criterion validity and convergent validity, as well as significant correlations of its subscales with related subscales of the MMPI.

PTSD Scale Checklist Civilian Version (PCL) (Weathers, Litz, Huska & Keane, 1994)

The PCL Scale is a tool for assessing post-traumatic stress. Built in 1994 by Weathers, Litz, Huska & Keane at the National Center for PTSD. It is a self-report questionnaire that includes 17 questions and statements, which explore the three categories of symptoms that occur during the development of post-traumatic stress, rejuvenation of the trauma, emotional numbness and anxiety and depressive symptoms. The statements statements are answered on a five-point frequency scale (where 1 = not at all, 2 = little, 3 = sometimes, 4 = enough and 4 = too much).

Aggression and Direction of Aggression Questionnaire (HDHQ) (Caine et al. 1967)

HDHQ is a self-administered questionnaire that measures aggression as an attitude. It is a test of measuring a wide range of possible manifestations of aggression.It reflects a willingness to respond with hostile behavior and a tendency to value people, including oneself, in an unfavorable and negative way. Aggression measured by HDHQ has nothing to do with physical aggression and physical violence. HDHQ consists of 5 subscales in the 52 items on the University of Minnesota Multiphasic Personality Inventory (MMPI). Three subscales, Impulsive Aggression (Actingout Hostility, AH), Criticism of Others (CO) and Paranoid Hostility (PH), refer to extroverted aggression. Two subscales, Self-Criticism (SC) and Delusional Guilt (Guilt, G), address introverted aggression and measure self-punishment. The sum of all five subscales reflects the overall aggression. Acceptable standards for total aggression in the normal population are between 12 and 14.

Statistical analysis

To analyze the demographic and psychometric characteristics of the sample, descriptive data of the distributions (mean and constant deviation (SD)) were used for their responses at each scale as well as at each subscale. The t-test was used to compare the two distributions because the tests for the regularity of the distributions through the Kolmogorov-Smirnov test but also through the regularity diagrams confirmed that the hypothesis of the regularity of the variables is acceptable.

In the cases of comparison of categorical data, the x2 test was used. Specifically, the following were used:

Pearson x^2 for 3x2 tables in cases where less than 25% of the expected values are <5,

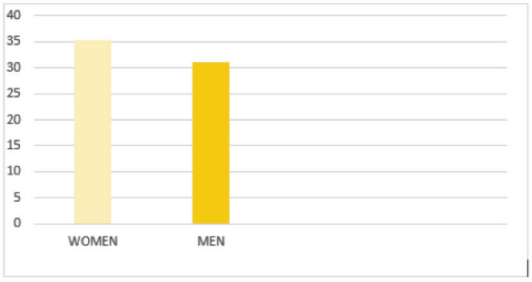
Pearson x^2 for 2x2 tables in cases where all expected values are> 10,

the Yates x^2 for 2x2 tables in cases where even one of the expected values is between 5 and 10,

Table: The variables by gender - means and standard deviations

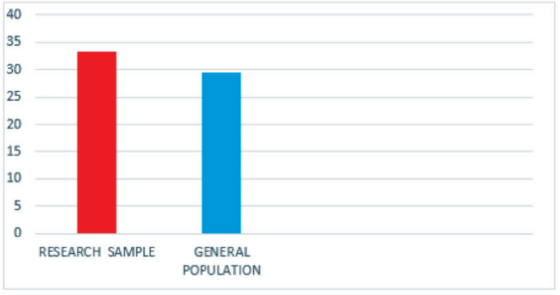
Hospitalization patients	Men		Women		
	Mean	SD	Mean	SD	
PTSD	34.52	18.03	42.85	9.38	p=0.001
PSYCHOPATHOLOGY	48.57	30.82	67.32	14.32	p=0.000

Mean values and Standard Deviations of PTSD in Hospitalitation patients(Men- Women)



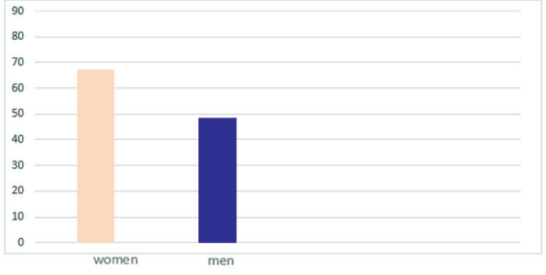
PTSD- Hospitalitation patients			
	N	Mean	SD
Men	77	31,02	18,03
Women	89	35,24	9,38

Mean values and Standart Deviations of PTSD in the research sample and in general population



PTSD		
	Mean	SD
Research sample	33,17	11,46
General population	29,4	12,09

Mean values and Standard Deviations of Psychopathology in Hospitalitation patients(Men- Women)



Psychopathology- Hospitalitation patients			
	N	Mean	SD
Men	77	48,57	30,82
Women	89	67,32	14,22

Pearson's parametric correlation coefficient (r) was used to investigate the statistical correlation of the quantitative variables between the two groups because the frequency distribution of their values was normal. The differences (P) for all indicators used were considered statistically significant from the level of 5% ($p < 0.05$). The statistical analyzes related to the descriptive characteristics of the variables were performed in Excel and SPSS programs, while the statistical analyzes related to the comparisons of quantitative and categorical variables as well as the correlations of the variables were applied to the SPSS statistical package.

Results

The results obtained from the correlation of the variables in pairs of the present study come to reinforce the results of other studies. In particular, the high correlations of post-traumatic stress, with gender, psychopathology, aggression, and hospitalization for covid19 as measured by PTSD, are consistent with the results of studies that report a linear correlation between the experience of a natural disaster and the occurrence of PTSD, but also with the results of studies that have found that post-traumatic stress is associated with conditions of an unpleasant lived experience (Gilbert & Miles, 2000; Gilbert et al., 2000, 2003; Goss et al., 1994).

The group of people who were hospitalized presented higher averages in terms of psychopathology such as: depression, paranoid ideation and interpersonal sensitivity, as well as the general symptom index and the overall score of psychopathology. No statistically significant differences were found between the two groups in the other subscales of the psychopathology questionnaire. These results support the hypothesis that patients with hospitalization have higher levels of psychopathology than those placed in quarantine. when a traumatic event occurs, both the fear response and the anger response can be activated simultaneously (Armor, et al., 2011).

Demographic characteristics of the sample

The mean age of hospitalized patients was 46.3 ± 5.8 and did not differ statistically significantly from the mean age of quarantined patients, which was 42.7 ± 6.5, compared with the t-test (P = 0,1). No statistically significant difference was observed between the sex composition of the two groups compared to Pearson's x^2 (P = 0,2). The highest percentages in both groups were men (54.7% hospitalization, and 62.3% simple quarantine). No statistically significant differences were observed between the two groups in the other demographic variables studied in the present study.

Psychopathology Scale (SCL-90)

The results showed that there was a significant difference between the two groups in terms of averages in depression (t = 2.173, p = 0.023) and paranoid ideation (t = 1.763, p = 0.032), while an indicative significant difference emerged in interpersonal sensitivity (t = 1.443, p = 0.037), in the general symptom index (t = 1.770, p = 0.082) and in the overall score of psychopathology (t = 1.109, p = 0.059).

PTSD Scale Checklist Civilian Version (PCL)

The results showed that there is a significant difference in the mean levels of post-traumatic stress disorder (t = 2.235, p = 0.012). The mean value of post-traumatic stress in the research sample was 33.17 ± 11.46 while the mean normal value of the levels of post-traumatic stress disorder in the general population is lower (29.4 ± 12.9) (Armor, et al., 2011).

Invasion and Direction of Aggression Questionnaire

The same pattern of results is observed in the aggression questionnaire. More specifically, the results showed that there is a significant difference in terms of averages in extroverted hostility (t = -2,010, p = 0.046) and total hostility (t = 1,844, p = 0.067) while in the other dimensions no statistically significant differences between the two groups were found.

Correlation analysis

The test for the existence of correlations of demographic factors and research questionnaires shows that gender is positively correlated with post-traumatic stress and the overall score in psychopathology. The experience of the disease in both groups is positively correlated with the symptoms of post-traumatic stress and especially aggression.

Gender differences

The t-test for independent samples was used to investigate differences in gender and age, post-traumatic stress, overall psychopathology and overall assessment of aggression. Significant differences were observed between the sex, regarding post-traumatic stress and overall psychopathology, while no statistically significant differences were found in age and aggression between the sex, as the size of the differences in the means was very small. Specifically in post-traumatic stress, the average of the post-traumatic stress scale, the average for men treated with covid19, was 31.08 ± (8.03), while for women treated, the average was 35.24 ± (9.38), with a statistically very significant difference between the two groups in their comparison with the t-test (p = 0.001). In the total score of psychopathology, the average of the total score of the psychopathology scale for men who declared that they were hospitalized was 48.57 ± (30.82), while for women, the corresponding average was 67.32 ± (14.32), with a statistically significant difference between the two groups in their comparison with the t-test (p = 0.000).

Discussion

In the present research study participated only individuals who became ill with covid19 and had simple hospitalization (not in an intensive care unit) in a Greek hospital-pandemic reference center or remained in compulsory confinement (quarantine) in a familiar environment for at least fourteen days, period of disease onset and the start of restrictive measures by the state (March - June 2020). The two groups of the sample differ in the manifestation of psychopathology, depression and mainly the appearance of symptoms of post-traumatic stress. The results show the appearance of

post-traumatic stress disorder, depression and anger in patients in the period immediately after their hospitalization. People who have been quarantined do not have similar disorders, which leads us to the conclusion that the conditions and special features of the disease that lead to hospitalization seem to create, among other things, a condition of psycho-traumatic event that increases the likelihood of post-traumatic stress disorder. This is in line with studies showing that the experience of life-threatening events causes mental disorders and stress and can lead to emotional problems in the period immediately following their expiration (Huber, 2003). Regarding the levels of post-traumatic stress disorder, it was found that women have higher levels of post-traumatic stress disorder than men, a result which is in agreement with similar studies (Armor et al., 2011). An attempt to interpret the high levels of hostility of hospitalized individuals could be based on Foulds (1967) view that high levels of hostility reflect difficulties in interpersonal relationships caused by a traumatic event. The deeper and mutually satisfactory interpersonal relationships people have with each other, the less likely they are to resort to extroverted or introverted hostility, even in cases of stress (Armor, et al., 2011). The results of the psychopathology correlations, as measured by SCL-90, of individuals in the covid 19 group treated with sex and post-traumatic stress agree with previous research highlighting the vulnerability of the female population as opposed to men (Armor et al., 2011).

Also, the results of the correlations of aggression, as measured by HDHQ, of people treated, post-traumatic stress disorder and psychopathology are in line with studies, which indicate that one of the ways in which people experience a psycho-traumatic fact, they try to protect themselves, is the manifestation of aggressive attitudes (Stemmler et al., 2007). Finally, the results of the present study agree with the findings of research that show that aggression functions as an autonomic reflex reaction and is a socialized form of post-traumatic stress disorder, associated with the manifestation of psychopathological behavior (Stemmler et al., 2007; Jarymowicz & Bar -Tal, 2006).

This research highlights a part of the special psychological profile of people suffering from coronary artery disease covid19, which becomes particularly important in the context of developing policies to promote, prevent and manage health problems arising from the pandemic.

Declarations

The authors declare that they have no conflicts of interest, that the work has been approved by the ethics committee responsible in the workplace, and do not declare means of financing of the work carried out.

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RESUMEN

Introducción: El propósito de este estudio fue investigar posibles trastornos mentales en pacientes que contrajeron Covid19 durante la pandemia de 2020 y fueron hospitalizados en un hospital griego (fuera de la unidad de cuidados intensivos) y su evaluación comparativa con los que ingresaron en cuarentena sin el inicio de síntomas graves covid 19. **Método**: El estudio involucró a 348 adultos de Grecia, a saber, 166 pacientes que fueron dados de alta después de la hospitalización en un hospital de referencia para pandemias y 182 individuos asintomáticos y no controlados que fueron puestos en cuarentena en un ambiente familiar durante el evento. pandemia. Resultados: Las personas que fueron hospitalizadas en el país por síntomas de covid 19, presentan en el período posterior al alta, trastornos mentales principalmente depresión y estrés postraumático. Aquellos que fueron puestos en cuarentena obligatoria no mostraron síntomas similares. Conclusiones: La naturaleza y características de la enfermedad covid 19, así como la simple hospitalización, parecen crear, entre otras cosas, trastorno de estrés postraumático y depresión que se manifiestan y siguen a los pacientes en el período posterior al alta. También parecen manifestarse síntomas de depresión y sentimientos de ira intensa. Estos resultados muestran una parte de los trastornos y psicopatología de los pacientes con covid19 tras su tratamiento. La manifestación de estos trastornos mentales parece estar relacionada con las condiciones específicas de la enfermedad pandémica, su extensión, intensidad, así como sus características como aislamiento social, mortalidad y contagio. La investigación, así como el tratamiento oportuno y adecuado del contexto de los trastornos mentales, especialmente el estrés postraumático y la depresión, deben recibir una atención especial y ser objeto de una investigación más amplia a lo largo del tiempo.

Bony pain management in cancerous patients

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ABSTRACT

Bone metastases develop in approximately 30–70% of all cancer patients. Pain is a universal human experience condition, and it is a common question for people to seek health care. The study aimed to describe the efficacy and roles of different strategies in the control of bony pain in metastatic cancerous patients. This is an observational study carried out, from the 1st of December 2018 to the 30th of December 2019. Exactly 100 cancerous patients were enrolled. Patients were assessed before received of pain control modalities, in the beginning, and at the end of treatment. Bone pain scoring was used from 0 (no pain) to 10 (the worst pain). Our findings regarding sex, there were 51(51%) male and 49(49%) female. The mean age was 57.3±11.2 years, and the most frequent age group was 41-50 years as 37(37%). Among cancer types, breast cancer comes in 1st rank cases studied in our research 37(37%), followed by prostate cancer 24(24%). Spine vertebrae were the most site figured 52%, followed by pelvic bones in 36%. Most patients did not require surgery. Whereas 15% of patients underwent cord decompression, 13% required internal fixation and only four patients performed for vertebroplasty. The sharp pain was commonly described by 40%, followed by stabbing nature in 15%. Frequent pain was more prevalent in 60% of patients, whereas constant pain presented in 40%. The night was the commonest timing of feeling pain in 55%. After receiving treatment, several modalities cause shifting of the pain scoring downward. Combination of more than strategies more efficient than of use one option for manage of bone pain with a better outcome, and prognosis.

Keywords: Bone metastasis, Pain scoring, Spinal cord decompression, Internal fixation, Bone pain

Introduction

Bone is the most common site of cancer metastasis, with an estimated 300,000– 400,000 US cancer patients affected by bone metastases (BM) each year[1], and it may be asymptomatic, they commonly cause significant morbidity and functional impairment due to pain, pathologic fracture, or spinal cord compression (SCC)[1, 2]. The workup of bone metastases includes a detailed pain history, physical examination, and relevant radiographic studies like plain x-ray, bone scan, CT scan, MRI, or PET[1].

Options include pharmacologic therapy, radiotherapy, systemic therapy (bisphosphonates, chemotherapy, hormonal therapy), and orthopedic surgery (including minimally invasive techniques such as vertebroplasty). Surgical treatment is most appropriate for patients with impending or established pathologic long-bone fracture, or impending or established SCC, assuming adequate performance status (PS) and life expectancy. Patients with SCC who had timely surgical decompression and postoperative RT have better outcomes, including higher rates of ambulation, compared with EBRT alone[1]. The orthopedic surgical modalities including Spinal cord decompression, fixation of the fracture, kyphoplasty vertebroplasty, and cementoplasty[1]. The goals in the treatment of include pain relief, preservation of mobility and function, prevention of future complications, optimized quality of life (QoL), maintenance of skeletal integrity, and minimization of hospitalization[1].

Radiotherapy was reported to be effective in palliating pain, with partial pain relief seen in 80-90% of patients and complete pain relief in 50%[2]. The response to treatment depends on a large number of factors, including sex, primary site, and histology, performance status, type of lesion, location of the metastases, weight-bearing vs non–weight-bearing site, the extent of disease, number of painful sites, marital status, and level of pain before treatment[2].

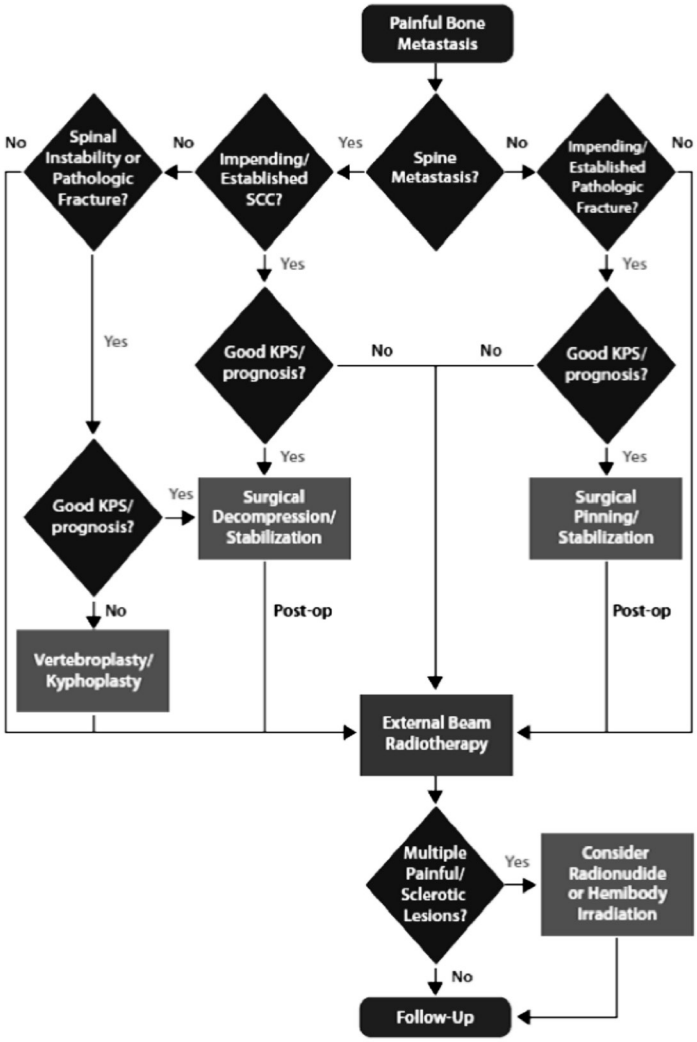
The most common symptom of bone metastases is slowly progressive, insidious pain that is fairly well localized. The pain may be worse at night. Pain from the femur or acetabulum may worsen with weight-bearing or ambulation. In contrast, pain from the inferior ischium or sacrum may be worse with sitting but less bothersome with ambulation. Although the pain is frequently localized, pain may radiate to other areas[3].

Palliative care is an approach that improves the QoL of patients and their families facing a life-threatening illness. It aims to prevent and relieve suffering by early identification, assessment, and treatment of pain and other physical, social, and spiritual problems. It affirms dying as a normal process and does not intend to postpone or hasten death. Palliative care offers a support system to help patients live as actively as possible until death[2, 4].

Pain is a universal human experience, and it is the most common question for people to seek health care. A patient whose pain cannot be cured or controlled might have an end-stage illness and he or she may live for months in pain[5]. At its best, pain is the body's natural alarm system, warning us of injury. The most widely accepted definition of pain is that given by the International Association for the Study of Pain (IASP): "Pain is an unpleasant sensory and emotional experience associated with potential or actual tissue damage or described in terms of such damage." Pain is always subjective, and it means that psychosocial and spiritual concerns can modify the sensation of it[6]. According to research by Sloan-Kettering Cancer Center, 78% of cancer-related pain is caused by the tumor, 19% is related to the treatment and 3% is not caused by cancer[5].

Despite increasing understanding about the effective treatment of pain, patients with pain from bone metastases frequently have inadequate pain management. Barriers to pain treatment include physician underestimation of the patient's pain and reluctance by the patient to report pain[7]. There is a significant discrepancy between the physician's estimate of pain and the pain level reported by the patient[7]. The use of a validated pain scale, such as the Brief Pain Inventory, allows the patient to describe the severity of pain and the interference of pain with function in a manner that can be understood both by the patient and the physician[7].

Figure 1. Flowchart of a management algorithm for bone metastasis.



Methods

This is an observational study carried out from the 1st of December 2018 to the 30th of December 2019. All patients recruited and exposed to SC decompression, internal fixation, and radiotherapy as palliative issues for pain control. All information about variables collected included age, tumor types, site of pain, words describe pain, characteristics of pain, timing of pain, medication relief pain, conditions interfering with pain as general activity, mood, work, sleep, enjoyment, concentration, and relationship with others.

About 100 patients, who were referred for pain control, enrolled in the study after informed consent was obtained from all patients. We catch eligibility criteria, and the sources and methods of selection of participants by using the questionnaires sheet, figure 2.

Patients were assessed before, at the beginning, and the end of treatment. For evaluation of pain relief, a numerical scale was used. This scores the pain from 0 (no pain) to 10 (the worst pain). Complete pain relief was defined as a complete absence of pain and without the need for analgesics. Partial pain relief was defined as the reduction of pain by a decrease in pain score of more than 2. Pain progression was defined as an increase in the pain score or increased medication use. The time to achieve pain relief was recorded from the day of treatment. The duration of pain relief was measured as the time from pain relief to the progression of pain or an increase in analgesic medication.

All variables were collected in an Excel sheet then transfer to statistical analysis into a file of "IBM SPSS Statistics" statistical package for social sciences version 24 (SPSS, Chicago, USA V 24). Frequencies and relative frequencies tabulation. Mean, and standard deviation describe the normal distribution. A two-sided *P* value of 0.05 or less and 95% confidence interval was considered statistically significant.

Results

Our findings regarding sex, there were 51(51%) male and 49(49%) female. The mean age was 57.3±11.2 years, and the most frequent age group was 41-50 years as 37(37%). Among cancer types, breast cancer comes in 1st rank cases studied in our research 37(37%), followed by prostate cancer 24(24%). Spine vertebrae were the most site figured 52%, followed by pelvic bones in 36%. Most patients didn't require surgery. Whereas 15% of patients underwent cord decompression, 13% required internal fixation and only four patients performed for vertebroplasty, (Table 1).

Bone pain manifestations are illustrated in (Table 2). The sharp pain was commonly described by 40%, followed by stabbing nature in 15%. Frequent pain was more prevalent in 60% of patients, whereas constant pain presented in 40%. The night was the commonest timing of feeling pain in 55%.

Figure 2. Pain questionnaires sheet.

Pain Questionnaire

1. Where is your pain?

   _____
   _____

2. Circle the words that describe your pain.

Aching	Sharp	Penetrating
Throbbing	Tender	Nagging
Shooting	Burning	Numb
Stabbing	Exhausting	Miserable
Gnawing	Tiring	Unbearable

3. Does your pain occur occasionally, frequently or is it constant? (Circle one)

   Occasionally Frequently Constant

4. What time of day is your pain the worst? (Circle one)

   Morning Afternoon Evening Nighttime

5. Rate your pain by circling the number that best describes your pain at its **worst** in the last month.

   No pain 0 1 2 3 4 5 6 7 8 9 10 Pain as bad as you can imagine

6. What makes your pain **better**? _____

7. What makes your pain **worse**? _____

8. What treatment or medication are you receiving for your pain? If you are not receiving any treatment or medication, circle NONE.

   None

9. Circle the one number that describes how, during the past week, pain has interfered with your:

   a. General Activity Does Not Interfere 0 1 2 3 4 5 6 7 8 9 10 Completely Interferes

   b. Mood Does Not Interfere 0 1 2 3 4 5 6 7 8 9 10 Completely Interferes

   c. Normal Work Does Not Interfere 0 1 2 3 4 5 6 7 8 9 10 Completely Interferes

   d. Sleep Does Not Interfere 0 1 2 3 4 5 6 7 8 9 10 Completely Interferes

   e. Enjoyment of life Does Not Interfere 0 1 2 3 4 5 6 7 8 9 10 Completely Interferes

   f. Ability to concentrate Does Not Interfere 0 1 2 3 4 5 6 7 8 9 10 Completely Interferes

   g. Relationships with other people Does Not Interfere 0 1 2 3 4 5 6 7 8 9 10 Completely Interferes

Table 1: Variables of the study.

Variables		No.	%
Sex	Male	51	51
	Female	49	49
Age (years)	30-40	5	5
	41-50	37	37
	51-60	25	25
	61-70	24	24
	>70	9	9
Tumor types	Multiple myeloma	6	6
	Lung	11	11
	Breast	37	37
	GIT	3	3
	Prostate	24	24
	Bladder	12	12
	CUP	7	7
Pain sites	Spine	52	52
	Pelvic	36	36
	Limbs	6	6
	Thorax	6	6
Orthopedic procedures	Spinal cord decompression	15	15
	Internal fixation	13	13
	Vertebroplasty	4	4
	No need	68	38

Table 2: Bony pain characteristics of this study.

Variables		No.	%
Descriptions	Aching	10	10
	Sharp	40	40
	Penetrating	5	5
	Burning	10	10
	Stabbing	15	15
	Exhausting	10	10
	Unbearable	10	10
Occurrence	Constant	40	40
	Frequent	60	60
Timing	Nighttime	55	55
	Daytime	45	45

Discussion

The bone demonstrated the most common site of causing pain[2], so most patients received palliation tools for bone secondaries. Radiotherapy has been proven to be an effective treatment for the palliation of symptomatic bone metastases in addition to the orthopedics modalities. The most common palliative doses for treating bone metastases are either a single 8 Gy or multiple fraction schemes such as 20 Gy in five fractions of 30 Gy in 10 fractions[2, 8, 9]. The single 8 Gy fraction or multiple fraction schemes are more effective at alleviating bone pain. Recent meta-analyses have shown equal efficacy between the different treatment regimens[3, 10, 11].

Bone metastases are a frequent complication of many cancers, particularly prostate, lung, and breast[10, 12]. They can lead to skeletal-related events, such as hypercalcemia, pathological fractures, spinal cord compression, and these requirements for either orthopedic intervention or radiotherapy[10, 12]. It is effective in reducing pain in two-thirds of patients, with about one-quarter of patients achieving a complete response[2, 3].

In 2007, Chow et al.[13] compared response rates for 16 randomized trials evaluating single versus multiple fraction regimens, this meta-analysis determined that there was equal efficacy of both single and multiple fraction treatment regimens.

Sharp, frequent, and night pain are commonly described. When assessing pain, patients should be asked to describe their pain, its quality, intensity, location, temporal pattern, and alleviating and aggravating factors[11]. The management of pain in cancer should be undertaken systematically, based on some principles. First, each pain should be assessed separately, and it should be ascertained that they are related to cancer[11].

WHO developed guidelines for the treatment of cancer pain in 1986 (revised in 1996), which were aimed at decreasing the prevalence of inadequate analgesia, this the most cause to used other options for alleviating pain in cancerous patients[4].

Conclusions

Most patients suffer from sharp, frequent, and night pain. After receiving palliative RT and/or orthopedic interventions the pain intensity shift to the minimum level.

Declarations:

The authors declare that they have no conflicts of interest, that the work has been approved by the ethics committee responsible

in the workplace, and do not declare means of financing of the work carried out.

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RESUMEN

Las metástasis **óseas** se desarrollan en aproximadamente 30 a 70% de todos los pacientes con cáncer. El dolor es una experiencia de la condición humana universal, y es común que las personas busquen atención médica a raíz de ello. El presente estudio tuvo como objetivo describir la eficacia y el papel de diferentes estrategias en el control del dolor **óseo** en pacientes cancerosos metastásicos. Se trata de un estudio observacional realizado entre el 1 de diciembre de 2018 y el 30 de diciembre de 2019. Se inscribieron exactamente 100 pacientes cancerosos. Los pacientes fueron evaluados antes de recibir las modalidades de control del dolor, al principio y al final del tratamiento. La puntuación del dolor **óseo** se utilizó de 0 (sin dolor) a 10 (el peor dolor). Nuestros hallazgos con respecto al sexo, hubo 51 (51%) hombres y 49 (49%) mujeres. La edad media fue de 57,3 ± 11,2 años y el grupo de edad más frecuente fue de 41-50 años, 37 (37%). Entre los tipos de cáncer, el cáncer de mama ocupa el primer lugar entre los casos estudiados en nuestra investigación 37 (37%), seguido del cáncer de próstata 24 (24%). Las vértebras de la columna fueron el sitio más representado en un 52%, seguido de los huesos pélvicos en un 36%. La mayoría de los pacientes no requirieron cirugía. Mientras que el 15% de los pacientes se sometieron a descompresión del cordón, el 13% requirió fijación interna y solo cuatro pa-

cientes se sometieron a vertebroplastia. El dolor agudo se describió comúnmente en un 40%, seguido de naturaleza punzante en un 15%. El dolor frecuente fue más prevalente en el 60% de los pacientes, mientras que el dolor constante se presentó en el 40%. La noche fue el momento más común de sentir dolor en el 55%. Después de recibir el tratamiento, varias modalidades provocan un desplazamiento de la puntuación del dolor hacia abajo. Combinación de más de estrategias más eficientes que utilizar una opción para el manejo del dolor **óseo** con un mejor resultado y pronóstico.

Ultrasound-Guided hydrodissection for treatment of Patients with Carpal Tunnel Syndrome

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ABSTRACT

The study aimed to compare Ultrasound-Guided Normal saline plus steroid hydrodissection group and Ultrasound-Guided normal saline alone hydrodissection group in patients with carpal tunnel syndrome (CTS), and to determine their clinical relevance in relation to treatment outcomes. We performed 60 US-guided hydrodissections Normal saline with and without corticosteroid injections in 51 patients with CTS and evaluated their pre- and post-injection US findings. We categorized these injections into two groups based on the normal saline plus corticosteroid (steroid group). normal saline (control group) and we also recorded clinical data including gender, age, side of injection, BW, and the duration of pre-injection CTS related discomfort. The outcomes were measured using the visual analog scale was assigned to assess the primary outcome. The secondary outcomes were assessed using the Boston Carpal Tunnel Syndrome Questionnaire, cross-sectional area of the median nerve, and electrophysiological studies. The assessment was performed prior to injection, and 1, 3, and 6 months' post-injection, and the symptom relief for the patients receiving normal saline and steroid injection were compared. We compared hydrodissections with normal saline and corticosteroid injections the clinical data, pre injection CSA-MN at the inlet of the carpal tunnel, and pre-injection BCTQ scores showed no significant intergroup differences ($p > 0.05$). All patients (data from 30 wrists in each group) completed the study. Compared both the control group, at all post-injection time points, both groups had a significant reduction in pain and disability, improvement on electrophysiological response measures, and decreased cross-sectional area of the median nerve. Our study reveals that ultrasound-guided Normal saline with and without corticosteroid hydrodissection has therapeutic effect in patients CTS. Nerve hydrodissection was shown to be potentially beneficial for CTS patients' pre-surgery. Hydrodissection is a simple, minimally invasive procedure that can be performed using only NS. In addition, compared to blind injection, hydrodissection under ultrasound guidance can lower the chances of nerve injury.

Key words: carpal tunnel syndrome, hydrodissection, corticosteroid, Normal saline injection, ultrasound guidance

Introduction

Carpal tunnel syndrome (CTS), involving compression of the median nerve (MN) deep to the flexor retinaculum, is one of the most common nerve entrapment syndromes encountered in musculoskeletal practice[1, 2]. The age distribution is bimodal with first peak in early 50s and second peak at age 75–84 years, and women, especially during pregnancy, are more commonly affected than men[3]. There are many causes and risk factors for carpal tunnel syndrome, such as trauma, vascular lesions, inflammation, obesity, occupational exposure, older age, osteoarthritis, pregnancy, hypothyroidism, or autoimmune diseases[4-8].

Pathophysiology of CTS is due to multifactorial causes, including nerve compression and traction disorders of the intraneural microcirculation, direct lesioning of the myelin sheath and axon, and alteration in the supporting connective tissue. Increased carpal tunnel pressure is thought to cause ischemic compression of the median nerve[9]. The severity of carpal tunnel syndrome can be divided into 5 levels, from very mild symptoms (pins and needles sensation, pain, or sensibility loss in the fingers and/ or hand, mostly only during night-

time) to continuously very severe symptoms (pins and needles sensation, pain, significant then atrophy, and/or significant sensibility loss in the fingers and/or hand, most time)[10].

Although ultrasound of the carpal tunnel can depict similar MRI criteria used in CTS, the most commonly evaluated parameter has been the median nerve cross-sectional area. Using the circumferential trace mode on the ultrasound screen, the cross-sectional area of the median nerve can

be measured. A widely accepted cutoff cross-sectional surface area for CTS with the highest sensitivity and specificity is 10 mm2, measured at the carpal tunnel inlet or pisiform. This sensitivity and specificity is high[11–14]. Although to avoid blind injection complications and for providing safer, reliable, and more efficient needle tip placement during CTS injections, ultrasound (US) guidance can play a beneficial role. Currently, musculoskeletal US has gained popularity based on its dynamic real-time property and low-cost availability[15]. Ultrasound provides high-resolution scanning view of median nerve and surrounding vessels and tendons and assists in diagnosis as well as needle placement guidance. Hence, there is a need for new intervention during the pre-surgical stages of CTS. Hydrodissection is a minimally invasive procedure of injecting fluid into anatomic spaces to facilitate dissection and adhesiolysis during surgery. injecting the material between the MN and transverse carpal ligament and underlying tendons which may interrupt the adhesions of MN and reduce the symptoms[16, 17].

Materials and Methods

Study design

This prospective, randomized, controlled, double-blind study was conducted between January 2017 and July 2018. In Nursing home in Baghdad Medical City and Private Pain Management Clinic. A total of 51 patients of them (total 60 wrists) were enrolled. Patients with suspected diagnosis of CTS were referred for this trial by orthopedic, neurologist and neurosurgery specialists. We obtained clinical history and performed physical examinations and electrophysiological studies. All patients signed informed consent and were block-randomized in a 1:1 ratio by drew random numbers from a sealed envelope. The patients were assigned to either a steroid group or a control group.

In the steroid group (n=30), patients underwent one session of ultrasound-guided median nerve hydrodissection with 1cc Triamcinolone 40 mg mixed with 5 cc normal saline (NS) total volume 6 cc. Patients in the control group (n=30) received ultrasound-guided guided median nerve hydrodissection with 6 cc normal saline (NS). If the patients were diagnosed as bilateral CTS, both wrists were assigned to the same group.

Any other conservative management regarding CTS therapy was prohibited from 2 weeks prior to initiation until 6 months post injection except for acetaminophen (500 mg, up to 2g per day), which was allowed for pain relief.

Inclusion and exclusion criteria

Patients, aged 20–80 years, diagnosed with mild-to-moderate CTS, with symptoms lasting for a minimum of 6 months, and confirmed by electrophysiological study, were enrolled. The definition of clinical symptoms/signs, and inclusion and exclusion criteria are presented in table 1 & 2[18].

The methods used for diagnosing and grading CTS based on electrophysiological study are presented in table 3 & 4[17-19].

Table 1. Inclusion criteria of symptoms and signs (Diagnosed as CTS if meeting criterion 1 with more than one of criteria 2 or 3 or 4).

Nocturnal paresthesia/dysthesia with or without pain over the subjected hand, which could be associated with posture or overuse of the wrist ; or relieved with shaking motion of the hand.
Numbness in the sensory distribution of MN.
Weakness with atrophic change of the MN-innervated thenar muscles.
Phalen's test (+) and/or Tinel's sign (+)

Table 2. Exclusion criteria (met anyone).

History of polyneuropathy, brachial plexopathy, thoracic outlet syndrome or wrist surgery
History of inflammatory arthritis, hypothyroidism, diabetes mellitus , pregnancy, and rheumatologic disorders or having pacemarker.
Current warfarin use, previous steroid injection for CTS, trauma or neoplasm at injection site, hypersensitivity to corticosteroid, skin infection (injection site).

Table 3. Electrophysiological Study Cut-off points or abnormal value.

1.Distal sensory latency of MN > 3.6ms (Stimulator: 14 cm distant from the active electrode at 2nd interphalangeal joints).
2.DML of the MN ≥ 4.3 ms (Stimulator: 8 cm distant from the active electrode at thenar muscle).

Table 4. Electrophysiological Study Grades.

History of polyneuropathy, brachial plexopathy, thoracic outlet syndrome or wrist surgery
History of inflammatory arthritis, hypothyroidism, diabetes mellitus , pregnancy, and rheumatologic disorders or having pacemarker.
Current warfarin use, previous steroid injection for CTS, trauma or neoplasm at injection site, hypersensitivity to corticosteroid, skin infection (injection site).

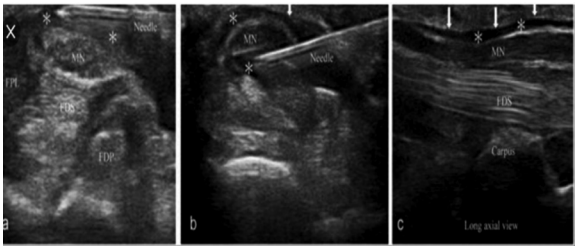
The US-guided injection technique was performed using the ulnar side approach. The patients were maintained a comfortable seated position with hands placed on a pillow, the forearm supinated and the wrist resting in a neutral position. In-plane ulnar approach was used for the US-guided CTS hydrodissection technique. Intervention was performed with a commercially available sonographic scanner (ALpinion,, the E-CUBE i7 with 10 to 12-MHz linear transducer).

The transducer was placed transversely along the distal wrist crease (transversely between the pisiform and the scaphoid bone) and perpendicular to the median nerve at carpal tunnel inlet (Figure 1). The flexor retinaculum was visualized as the hyperechoic structure forming the carpal tunnel roof across the pisiform and scaphoid bones. The median nerve lies just below the flexor retinaculum, the ulnar nerve and artery were detected just radial to the pisiform outside the carpal tunnel. Doppler imaging can be used to confirm the artery location if necessary. The injection was performed under sterile conditions with an in-plane freehand technique. After skin preparation with an antiseptic chlorhexidine 2%, the proximal carpal tunnel was visualized with the same transducer. A sterile US transducer cover and pajunk echogenic 50 mm 22G Needle was used. Needle entrance anesthetized with 1 cc xylocaine 1% then inserted into the skin from the ulnar side of the proximal carpal tunnel at the level of the distal wrist crease. The needle passed to skin nearly parallel with the transducer. It traverses superficially to

Figure 1. Sterile US transducer cover and pajunk echogenic 50 mm 22G Needle was used.

the ulnar nerve and artery, penetrating the flexor retinaculum. Under real-time ultrasound-guide median nerve hydro dissection with 1cc Triamcinolone 40 mg mixed with 5 cc normal saline (NS) total volume 6 cc or 6cc NS. 3 cc inject was injected to hydro-dissected the MN from the flexor retinaculum, and the residual 3 cc inject was then injected to hydro-dissected the inferior MN away from flexor tendons.

Figure 2. Hydrodissection the the inferior MN from the flexor retinaculum and hydro-dissected MN away from the flexor tendons.



After injection, the operator scanned hrough the whole carpal tunnel to confirm the delivery of inject throughout the tunnel hydrodissection the MN from the flexor retinaculum and hydro-dissected the inferior MN away from the flexor tendons.

Every patient was observed for half an hour after injection for any complications, such as nerve trauma, ecchymosis or bleeding etc., before discharge.

Outcome measurements

We performed all outcome assessments, without knowledge of which group patients were in or the injectate content, at 1, 3, and 6 months post-injection, for comparison with pre-injection measures Outcome Measurements.

Primary outcome

Visual analog scale (VAS)

The severity of digital pain or paresthesia or dysesthesia within one week before evaluation was recorded using VAS, with the score ranging from 10 (tremendous pain) to 0 (no pain)[20]. A minimum decrease of 1.3 points in VAS or 25% reduction in pain is considered the minimal clinically important difference for pain intensity.

Secondary outcome

Secondary Outcome: Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) Score. The self-administered BCTQ includes 2 subscales of symptom severity (11 questions) and functional status (8 questions); it is the most commonly used measurement for CTS. Scores range from 0 to 5 points for each question, with higher scores indicating greater severity and dysfunction.

Secondary Outcome

Cross-sectional Area (CSA) of the MN. *circumferential trace mode on the ultrasound screen, the cross-sectional area of the median nerve can be measured*. In brief, the CSA was measured using an electronic caliper at the proximal inlet of the carpal tunnel (ie, at the scaphoid-pisiform level). The mean of 3 such measurements was used for analysis.

Electrophysiological Analysis Results. The anti-dromic sensory nerve conduction velocity (SNCV) and distal motor latency (DML) of the MN were measured in all patients as described elsewhere. In brief, the SNCV was measured using a 14-cm stimulator that was proximal to the active electrode over the second inter-phalangeal joint. The DML was recorded via MN stimulation at 8 cm proximal to the active electrode over the abductor pollicis brevis muscle. An average of 3 such measurements was calculated.

Statistical Analyses

All data were analyzed using IBM SPSS software, version 22. Demographic data were analyzed using an independent t-test for continuous data, and Fisher exact test for categorical data. A repeated-measures analysis of variance and a subsequent post hoc test were used for analysis of the follow up data. An independent t-test was performed to compare differences between groups, including VAS scores, BCTQ scores, CSA of MN measurements, electrophysiological study results, and global assessment results. All statistical tests were 2-tailed; a P value of less than 0.05 was consider statistically significant.

Results

During a 18-month period (January 2017 and July 2018), 79 carpal tunnel injections were undertaken in 70 patients with CTS. 19 patients were excluded because loss of follow-up US examinations (19 injections in 19 patients). In total, we included 60, injections that were performed in 51 patients (Figure 3). Clinical characteristics of the participants did not differ between groups (Table 5). All results showed in tables 6-10. The mean duration of symptom onset was 31.54±6.54 and 32.73±5.73 months in the normal saline plus Steroid hydrodissection Group and normal saline alone hydrodissection Group, respectively.

Table 5. Baseline Demographic and Clinical Characteristics of Study Participants.

Characteristic	Normal saline plus Steroid hydodissection Group N(30 wrist)	Normal saline hydrodissection Group N(30wrist)	P value
Age (y)	52.74±3.23	52.53±2.56	<0.90
Body height (cm)	157.16±2.25	156.14±1.32	<0.73
Body weight (kg)	68.21±1.7	69.12±1.2	<0.70
Duration (months)	31.54±6.54	32.73±5.73	<0.99
Gender N Male Female	 2 28	 1 29	<0.83
Lesion sits Right Left	 18 12	 16 14	<0.97
Grading Mild Moderate	 15 15	 13 17	<0.89
BCTQS Severity functional	 29.25±1.53 21.56±0.65	 28.52±2.03 19.28±0.43	 <0.45 <0.26
VAS	6.891±0.41	6.45±0.36	<0.99
CSA(mm²)	12.54±0.45	12.63±0.36	<0.51

BCTQ=Boston Carpal Tunnel Syndrome Questionnaire severity and function, data were analyzed using an Independent t test, Chi-square test or Fishers exact test.

Table 6. the Visual analog scale score.

Visual analog scale score	Normal saline plus Steroid hydodissection Group N(30 wrist)	P value	Normal saline hydrodissectio n Group N(30wrist)	P value
Before injection	6.89±0.41		6.45±0.36	
Month 1	4.73±0.37	<0.001	5.42±0.21	<0.001
Month 3	3.29±0.35	<0.001	3.69±0.51	<0.001
Month 6	2.89±0.21	<0.001	2.59±0.37	<0.001

Both group exhibited a significant reduction in pain and disability became more pronounced as the follow-up duration increased revealed significant improvement for VAS in both group data were analyzed using an Independent t test, Chi-square test or Fishers exact test.

Table 7. Boston Carpal Tunnel Syndrome Questionnaire score.

Boston Carpal Tunnel Syndrome Questionnaire score	Normal saline plus Steroid hydodissection Group N(30 wrist)	P value	Normal saline hydrodissection Group N(30wrist)	P value
severity	Mean ± standard error		Mean ± standard error	
Before injection	29.25±1.53		28.52±2.03	
Month 1	20.68±1.05	<0.001	24.20±1.03	<0.001
Month 3	16.20±1.46	<0.001	17.20±2.63	<0.001
Month 6	14.16±0.87	<0.001	15.20±1.82	<0.001
Functional	Mean ± standard error		Mean ± standard error	
Before injection	21.56±0.65	<0.001	19.24±0.43	
Month 1	13.20±1.43	<0.001	16.20±1.09	<0.001
Month 3	12.20±1.03	<0.001	14.20±1.54	<0.001
Month 6	11.20±1.65		12.20±1.85	<0.001

Both group exhibited a significant reduction in Boston Carpal Tunnel Syndrome Questionnaire score for severity and function became more pronounced as the follow-up duration increased revealed significant improvement.

Table 8. Electrophysiological study

Electrophysiologic al study	Normal saline plus Steroid hydodissection Group N(30 wrist)	P value	Normal saline hydrodissection Group N(30wrist)	P value
Sensory nerve conduction velocity (m/s)	Mean ± standard error		Mean ± standard error	
Before injection	33.56±1.03		33.79±0.83	
Month 1	35.68±1.05	0.04	34.20±1.03	0.99
Month 3	36.20±1.03	0.003	36.70±1.13	0.003
Month 6	36.16±1.17	0.004	36.14±1.82	0.004
Distal motor latency (ms)	Mean ± standard error		Mean ± standard error	
Before injection	4.86±0.63		4.68.±0.16	
Month 1	4.72±0.21	0.22	4..70±0.15	0.51
Month 3	4.64.±0.22	0.53	4.72±0.15	0.32
Month 6	4.53.±0.26	0.20	4.5±0.17	0.43

Found that both groups had significant electrophysiologic improvement immediately after hydrodissection, showed improvement in nerve conduction values as the follow-up duration increased.

Table 9. Complications.

Complications	Normal saline plus Steroid hydodissection Group N(30 wrist)	Normal saline hydrodissection Group N(30wrist)
nerve insult N	0	0
vessel insult N	2	0
lesion (eg, color change) N	5	3
Infection N	0	0

Figure 4. Mean change at baseline and post-injection in visual analog scale results in both groups (mean standard error). The visual analog scale scores were significantly lower in the both groups, at all follow-up assessments (P<0.05), and this reduction became more pronounced as the follow-up duration increased an independent t-test was used.

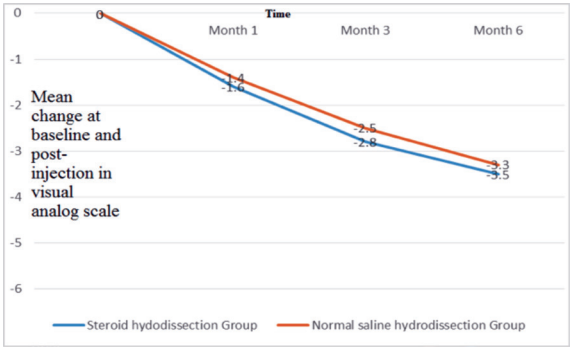


Figure 5. Mean difference at baseline and post-hydrodissection in Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) scores(severity) in both groups (A) The BCTQ scores were significantly lower, indicating improvement at all follow-up assessments (P<0.05).

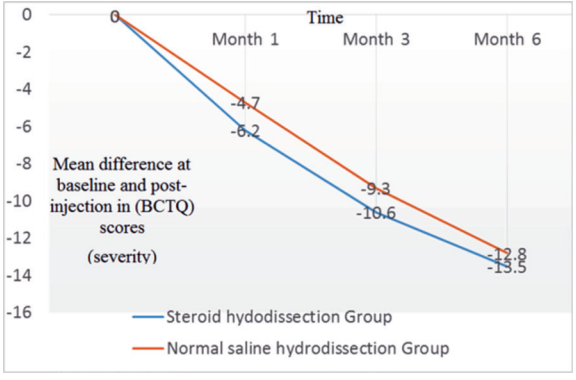
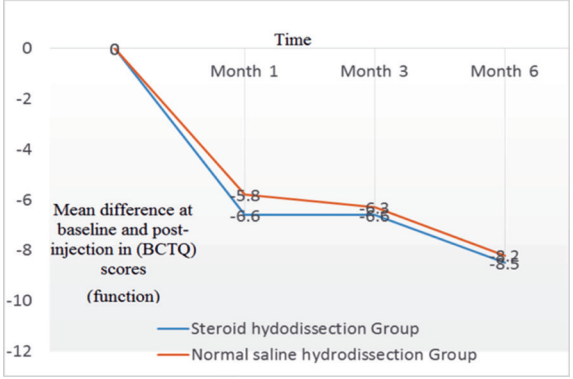


Figure 6. The BCTQ (function) scores were significantly lower, indicating improvement, in both groups, at all follow-up assessments (P<0.05). All differences became more pronounced as the follow-up duration increased.



We checked complication after injection, including nerve insult, vessel insult, and skin lesion (eg, color change). Infection in both groups: 2 patients in Normal saline plus Steroid hydodissection Group. N (30 wrist) had vascular insult that resolve after two days of procedure. 5 patients in Normal saline plus Steroid hydodissection Group. N (30 wrist) had ecchymosis that resolved after one week of procedure compare with 3 patients in control group.

Discussion

The present study is prospective, randomized, controlled study to compare the benefit of Ultrasound-Guided Normal saline plus steroid hydro dissection group and Ultrasound-Guided normal saline alone hydro dissection group in patients with carpal tunnel syndrome (CTS) both groups exhibited a significant reduction in pain and disability, an improved electrophysiological response, and a decreased CSA of the MN for 6 months after treatment.

Our technique provided direct visual guidance under US, as well as actual separation of the MN from the compressing flexor retinaculum throughout the carpal tunnel by hydrodissection.

Evers et al demonstrate that, in a cadaver preparation, infiltration of saline into the carpal tunnel can reduce the resistance to longitudinal sliding of the median nerve This experiment was prompted by recent interest in the concept of 'hydrodissection' for the treatment of carpal tunnel syndrome[21]. This can be traced back to a 2008 Smith J et al paper describing an ultrasound guided approach to the familiar procedure of corticosteroid injection for CTS in which the needle is inserted from the ulnar border of the wrist, transversely into the carpal tunnel[22], The authors speculated that the infiltration of inject between the median nerve and transverse carpal ligament, and between the median nerve and underlying tendons "may disrupt adhesions". Since then, enthusiasts for ultrasound guided carpal tunnel injection have adopted the idea that they are breaking adhesions between the nerve and surrounding structures as an established fact. The term 'hydrodissection' has

become common place in descriptions of ultrasound guided carpal tunnel injections, and the technique has even been described in a recent textbook as being useful for disrupting adhesions, especially after surgery[23].

The first thing which is notable about all of the above-mentioned papers is that in every case the hydrodissection procedure is carried out with an inject containing between 40 and 80 mg of methylprednisolone, or an equivalent amount of an alternative steroid. Corticosteroid injection is known to be markedly effective in the short term as a treatment for CTS, with approximately 80% of patients reporting benefit from injection, even when the injection is not ultrasound guided and no attempt is made at hydrodissection[24-26]. It should therefore procedure confers additional benefit over and above corticosteroid injection without hydrodissection, or alternatively that hydrodissection alone, with saline, has a therapeutic effect superior to that of a placebo injection, in which saline would be injected just proximal to the carpal tunnel with the same ultrasound guidance.

Injection-related placebo effects and spontaneous remission of CTS could contribute to the therapeutic effects in our study. Unfortunately, the individual contribution of the placebo effect vs. nerve hydrodissection is hard to differentiate as the minimal volume of inject that is necessary for a significant effect of nerve dissection is unknown. Wu et al.,[27] found that ultrasound-guided perineural injection with 5 cc NS could improve symptoms 6 months' post injection in patients diagnosed with mild-to-moderate CTS compared with their baseline.

Malahias et el.,[24] also reported that 33% of patients showed clinical improvement 12 weeks post ultrasound-guided perineural injection of 2 cc NS. Nevertheless, the injection-related placebo effect was stronger than the placebo effect after a non-interventional procedure. Kirwan et al., have shown almost 30% pain reduction from placebo effect within the first few weeks after intra-articular injection for patients with knee osteoarthritis[28]. A recent meta-analysis, however, demonstrated statistically and clinically significant improvement 6 months post intra-articular injection of NS for knee osteoarthritis[29].

Additionally, the possibility of spontaneous remission in these prior studies cannot be completely excluded. Padua et al.,[30] revealed that patients with untreated CTS showed between 27% and 34% symptomatic improvement after 10 to 15 months' follow-up in a prospective study.

Ortiz-Corredor et al.,[31] demonstrated that 25% and 47.6% of untreated patients with CTS showed electrophysiological improvements and symptom recovery respectively in a 2-year follow-up study. Because we used a uniform injection procedure and injectate volume in a randomized, double-blind, controlled trial, the possible concurrent effect of placebo effect and spontaneous remission cannot be ignored in our study.

In our study, we found that the majority of parameters of BCTQ improved in both groups at the initial follow-up time point. As the effect of nerve hydrodissection is postulated to be initiated at early follow-up time points, this result was unexpected. The injection-related placebo effect may influence the initial therapeutic effect in both groups making it hard to distinguish the intergroup differences until progressive nerve regeneration which often occurs at later stages after hydrodissection. Peripheral nerve regeneration is a relatively slow process, proceeding at a rate of 1 mm/day in humans. One study showed re-innervation of the thenar eminence by the median nerve after carpal tunnel release (CTR) of at least 12 months[32]. In a cohort study of 45 patients with mild, moderate, and severe CTS, individuals were treated with CTR and a postoperative electrophysiologic evaluation was performed 2 weeks, 2 months, and 6 months after surgical decompression. The authors found that the mild group had significant electrophysiologic improvement immediately after decompression. The moderate group showed marked improvement in nerve conduction values in all cases. In the severe group, electrophysiologic improvement was seen, but normalization of electrophysiologic test values were only possible in a few patients[33]. Extrapolating from this study, it would be safe to assume 6 months to be adequate for repeat electrodiagnostic testing.

We think that the effect of hydrodissection-induced mechanical remobilization of the

MN may be brief because NS does not have any additional pharmacological effect. We hypothesized that the initial therapeutic effect may result from the mechanical hydrodissection and that subsequent nerve regeneration would contribute to the observed long-term effect. In contrast to BCTQ, CSA is an objective measure that would be unaffected by injection-related placebo effect. We observed significant decreased CSA between the two groups from 1 month post injection through all follow-up time points. These findings may indicate that the effect of nerve hydrodissection can be observed as early as 1 month post injection. However, Peters-Veluthamaningal et al.,[34] found that 5 of 33 (15%) patients exhibited a satisfactory partial response at a follow-up assessment at 1 week after a 1-cc normal saline injection. Girlanda et al.,[35] reported notable improvement in nocturnal paresthesia and motor action potential at up to 2 months after a 15-mg normal saline injection (9 mg/cc; 2 injection sessions with a 1-week intervening interval).

The effect of normal saline injection in our study was longer and more pronounced, compared with the effects in the aforementioned research, possibly owing to differences in the guided method or inject volume. Our study was the first to use ultrasound guided injection with normal saline for the control group, and the 6 cc of inject was a greater volume than that used in previous studies. A direct compression of the transverse carpal ligament at the MN induces CTS, and CTS subsequently induces inflammation of the intra-carpal tendon. This condition commonly causes a cycle of swelling within the carpal tunnel and further compresses the MN[36]. Moreover, compared with blind injection, ultrasound- guided nerve hydrodissection is better for removing surrounding tissues from the MN, especially the intra-carpal tendons.

Limitations

Our study has some limitations. First, the small patient group with female predominance and the lack of long-term follow-up.

Second, we were not able to determine the influence or most appropriate timing of nerve hydrodissection. the recurrence rates and long-term effects of treatment are unknown. Further research should include longer study periods to determine nerve hydro dissection has therapeutic effect in patients with mild-to-moderate CTS, additional benefit for the long-term CTS treatment and to verify the effects of reducing recurrence.

Finally, the optimal dosage and number of hydrodissection. sessions is unknown, so further studies are needed

Conclusion

This study demonstrates that nerve hydro dissection has therapeutic effect in patients with mild-to-moderate CTS. Nerve hydrodissection was shown to be potentially beneficial for CTS patients pre-surgery. Hydrodissection is a simple, minimally invasive procedure that can be performed using only NS. In addition, compared to blind injection, hydrodissection under ultrasound guidance can lower the chances of nerve injury. Moreover, the cumulative effect of hydrodissection is expected after repeated injections, and hydrodissection may also have possible advantages for post-operative adhesion in patients with CTS.

Recommendation

In future research, nerve hydrodissection could be compared with traditional management techniques, e.g., splint, physical therapy and its effect could be studied in CTS patients with post-operative adhesions or unsuccessful surgery. Further studies are also needed to prove the effect of this technique for other entrapment neuropathies.

Abbreviations and Acronyms:

BCTQ= Boston Carpal Tunnel Syndrome Questionnaire; CSA= cross-sectional area; CTS= carpal tunnel syndrome; DML= distal motor latency; MN = median nerve; SNCV= sensory nerve conduction velocity; VAS= visual analog scale, MN= median nerve; SNCV= digit/wrist sensory nerve conduction velocity; DML= distal motor latency

Declarations:

The authors declare that they have no conflicts of interest, that the work has been approved by the ethics committee responsible in the workplace, and do not declare means of financing of the work carried out. Informed consent was obtained to publishing these cases.

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RESUMEN

El estudio tuvo como objetivo comparar el grupo de hidrodisección de solución salina normal guiada por ultrasonido más esteroides y el grupo de hidrodisección de solución salina normal guiada por ultrasonido sola en pacientes con síndrome del túnel carpiano (STC), y determinar su relevancia clínica en relación con los resultados del tratamiento. Realizamos 60 hidrodisecciones guiadas por ecografía con solución salina normal con y sin inyecciones de corticosteroides en 51 pacientes con STC y evaluamos los resultados de la ecografía antes y después

de la inyección. Clasificamos estas inyecciones en dos grupos según la solución salina normal más corticosteroide (grupo de esteroides). solución salina normal (grupo de control) y también registramos datos clínicos que incluyen el sexo, la edad, el lado de la inyección, el peso corporal y la duración de las molestias relacionadas con el STC antes de la inyección. Los resultados se midieron mediante la escala analógica visual que se asignó para evaluar el resultado primario. Los resultados secundarios se evaluaron mediante el cuestionario del síndrome del túnel carpiano de Boston, el área transversal del nervio mediano y estudios electrofisiológicos. La evaluación se realizó antes de la inyección y 1, 3 y 6 meses después de la inyección, y se comparó el alivio de los síntomas de los pacientes que recibieron la inyección de solución salina normal y de esteroides. Comparamos las hidrodisecciones con la solución salina normal y las inyecciones de corticosteroides; los datos clínicos, la preinyección de CSA-MN en la entrada del túnel carpiano y las puntuaciones de BCTQ antes de la inyección no mostraron diferencias significativas entre los grupos (p> 0,05). Todos los pacientes (datos de 30 muñecas en cada grupo) completaron el estudio. En comparación con el grupo de control, en todos los momentos posteriores a la inyección, ambos grupos tuvieron una reducción significativa del dolor y la discapacidad, una mejoría en las medidas de respuesta electrofisiológica y una disminución del área transversal del nervio mediano. Nuestro estudio revela que la solución salina normal guiada por ecografía con y sin hidrodisección de corticosteroides tiene un efecto terapéutico en los pacientes con STC. Se demostró que la hidrodisección nerviosa es potencialmente beneficiosa para los pacientes con STC antes de la cirugía. La hidrodisección es un procedimiento simple y mínimamente invasivo que se puede realizar utilizando únicamente NS. Además, en comparación con la inyección a ciegas, la hidrodisección bajo guía ecográfica puede reducir las posibilidades de lesión nerviosa.