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Potential Role of Synesthesia in Combatting Neurodegenerative Diseases

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Abstract:

This research aims to draw a bridge between synesthesia as a method of studying consciousness and the techniques that are used to combat neurodegerative disorder. We do not claim that the sole induction of synesthesia would help improve dementia but its integration with the conventional management of dementia treatment would definitely lead towards a better prognosis. Synesthesia is the crossing of senses such that external stimuli aimed at one sensory modality will elicit a response in another sensory modality. There are approximately 80 different kinds of synesthesia. Though this phenomenon is being investigated upon since 1880 there still exists concepts which are blurry. According to study conducted on the induction of synesthesia, it is a latent feature in all individuals, manifesting when the balance of activity across the senses has been altered.(Nair & Brang, 2019)

Through this article, we are attempting to enforce synesthetic induction in patients with dementia (beginning with mild dementia) and are suggesting that Synesthetic training can be provided to people who have higher predisposition to dementia if feasible. Moreover, we have modified the existing experimental trial for synesthetic training and induction to make them more compliant with patients suffering with dementia. Here it is necessary to mention that we just have the experimental therapy design in theory and in no way have we tried to execute it. If we are provided with more time and resources, we will be more than willing to conduct the procedure.

In addition, our study includes an observational analytic research which follows a cohort design. We have collected data from 102 individuals to establish the association between the synesthesia-like capabilities and lower predisposition of neurodegenerative disorders. If this association is true, our survey form can be used to better identify populations with predisposition to dementia and also start synesthesia training in marked individuals.

Keywords- stroop's test, aphantasia, cortical pruning, neural plasticity

Introduction:

This vast subject, in spite of being an archaic phenomenon, is still being extensively studied currently and many of its aspects are yet to be understood and unfolded. Synesthesia in simple terms is the cross linking of senses which is experienced by mere 4.4 percent of the world's

population. The stimulation of one sense causes response in another. The stimulated percept is called the inducer whereas the additional perceived percept is called the concurrent (Grossenbacher & Lovelace, 2001). Essentially some people see colour projecting in the space around them (usually diagonally) when they hear music. Each chord (combination of harmonic notes) has a distinct colour. This kind of synesthesia is called chromesthesia. Another kind in which the individual associate's text or symbols to particular colours is called grapheme synesthesia. The synesthetes either observe the colours projecting out in their spatial surroundings or distinct image of the colour forms inside their mind. The former is termed as projection synesthesia while the latter is called association synesthesia. It is important to mention here that synesthetes are aware of the ordinal colour of the text/symbol. If the text is black then the association forms immediately, if the colour of the text is congruent with the one that individual has association with then there is no question of difficulty in its perception but if the colour of the text is incongruent with the colour in synesthete's perception then this causes interference and is the reason why synesthetes demonstrate exaggerated delay in stroop's test (Mills, Boteler, & Oliver, 1999).

People with spatial sequence synesthesia observe time as a spatial phenomenon. They see days of the week/ months/ years as having distinct shapes and forms in space around them. For example, Monday may look like a pentagon while the year 1993 maybe a sphere. Number form synesthetes can see a mentally devised map of numbers for any given set of consecutive numbers either project out in the space or in their "mind's eye". A tingling /caressing sensation i.e., a tactile stimulus will follow certain syllables or sounds in people with auditory tactile synesthesia (Ward et al., 2008). Some people link personality traits and quirks to numbers and letters. This could include gender identity or age. For example- 6 could be a bubbly, talkative 9-year-old girl while D could be a dementic old lady. This type is termed as ordinal linguistic personification synesthesia. Certain sounds or syllables can trigger particular emotions (conventionally negative) in people who have misphonia, another kind of synesthesia. Moreover, certain syllables or sounds could also illicit a particular taste in someone's mouth in a rare form of synesthesia called lexical gustatory synesthesia (Ward and Simner, 2003). Aforementioned are the most common types of synesthesia.

Synesthetes have better visual perception and short-term memory as compared to the general population. However, there is absence of a significant difference in long term memory between the two (anomaly for treatment of dementia, justified in the 'Limitations' section of the article).

Literature review-

Approximately 80 kinds of synesthesia have been documented yet. This question the prevalence of this phenomena as being as rare as 4.4% of the population. Many studies suggest otherwise. But neither are the guidelines of diagnosis as concrete as previously assumed. The diagnostic criteria include automaticity (immediate association) and consistency (same pattern of colour/ spatial orientation throughout life) and idiosyncrasy (Cytowic, 2002) i.e., inter-individual variance. However, research proves that synesthetic capabilities decrease with increasing age (Simner et al., 2017), additionally consistency varies with familiarity of the grapheme, less familiar grapheme show less consistency(Uno et al., 2021). These anomalies take us to the purpose of our research. We believe that practically applying synesthesia will help us gain more knowledge about it. There are various methods via which a non synesthete can become a synesthete.

1.Induction(Nair & Brang, 2019)

2.Training(Bor et al., 2014)

3.Acquisition by psychedelic drugs and brain lesions/sensory deafferentation.

The former two will be discussed in the modified experimental therapy for patients with dementia.

Genuine and brain injury acquired synesthesia point to morphological substrates, while drug-induced synesthesia appears to be based on functional changes of brain activity and is also short term.

In the case of psychedelic drugs there are no consistent inducer-concurrent couplings (Beringer, 1927; Friedrichs, 2009). The automaticity can't be judged either. A particular inducer may or may not illicit a response. Most hallucinogens modify activity in two areas: the locus coeruleus (LC) and pyramidal cells in the cortex (Aghajanian & Marek, 1999).

While in the case of acquisition by brain injury, the consistency is subjective to the patient. There is same concurrent for different inducers hence some level of consistency exists but if the number of concurrent increases, then the inducer-concurrent consistency is not maintained. In the studied cases, automaticity is reduced. For example, the induction occurs only 4 out of 5 times when a synesthetic stimulus is applied. Often concurrent last for only a split second. The brain injury leads to dissociation of certain neuronal communication pathways followed by

compensatory reorganization in the remaining pathways indicating increased neuronal plasticity. Another theory is that because decreased sensor input to thalamus, there is unmasking of pre-existing pathways.(Sinke et al., 2012).

The following table briefly describes the existing theories of synesthesia-

Theory	**Author**	**Explanation**	**Additional Notes**
Hyperconnectivity Theory	Ramachandran and Hubbard	Caused by increased connectivity between cortical regions.	Connectivity is likely caused by failure of cortical pruning of neurons.
Disinhibition-unmasking hypothesis	Grossenbacher and Lovelace	Caused by a decreased level of feedback from inhibitory cortical areas.	This theory suggests constitutive inhibitory cortical feedback is present in everyone.
Learned association theory	Calkin	Suggests that synesthetic links are caused by learned associations early in life.	Discredited due to genetic component and increased incidence in women.
Awareness theory	Cytowic	Suggests that synesthesia is part of a normal perceptual process, and the phenomenon is caused by a failure of our brain to suppress the concurrent which he	Implicates the limbic system as important especially the hippocampus.

		hypothesizes occurs in everyone.	
Neonatal synaesthesia	Maurer	This theory suggests that humans are all born with synesthesia-like tendencies, which in "normal" people are lost through age.	Widely refuted.

Table from (Harvey, 2013). Behaviour and neuroimaging both of demonstrate functional cross-activation but cannot explain the mechanism for the hyperconnectivity.

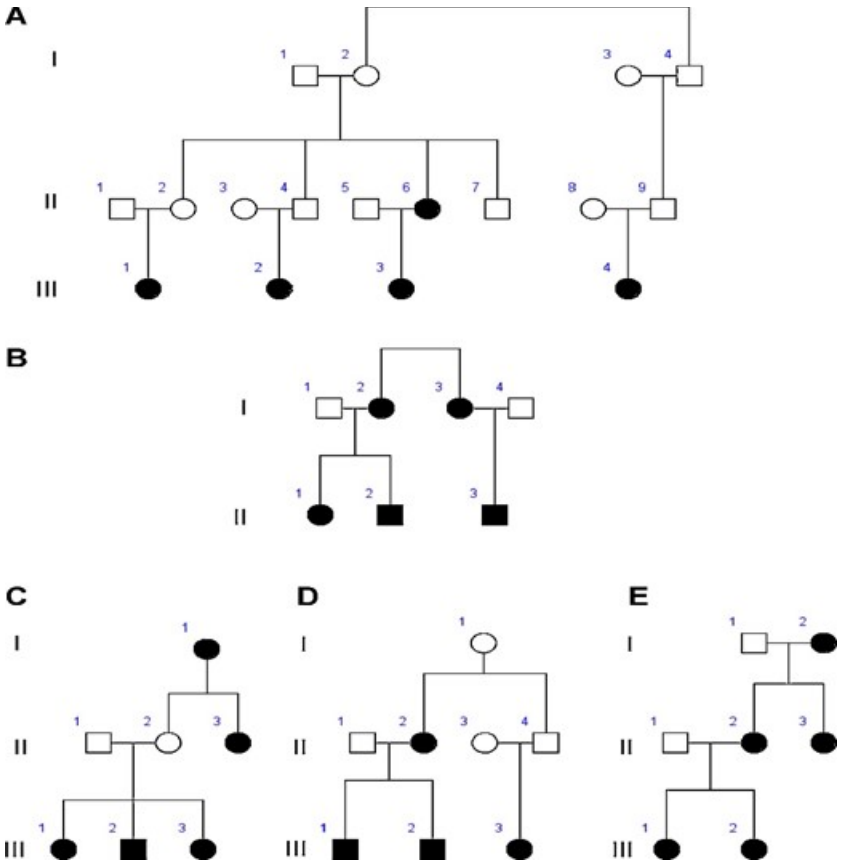
Neuroanatomical aspects of synesthesia

Paulesu et al. (1995) used positron emission tomography (PET) to measure brain activation in six sound-vision synesthetes and six controls and found evidence of feedback links between the visual cortical regions and higher order cortical regions (occipital and parietal cortical regions, the bilateral inferior temporal gyrus, and the left lingual gyrus). Additionally, this study indicated that V1(primary visual cortex) and V4(extra striate cortex) are less important. Moreover, disruption via transcranial magnetic stimulation in the right parietal lobe but not V1 or the left posterior parietal cortex reduced synesthesia (Esterman et al., 2006). However significant activity was detected in primary visual cortex, in the absence of external visual stimulation in a functional-mri case study(Aleman et al., 2001). Studies have also proposed that basis of sequence space synesthesia may be the close proximity of temporal lobe regions implicated in sequence coding and visual object representation(Eagleman, 2009).

Genetics associated

Synesthesia runs in families. Analyses of pedigrees suggest that the genetic component(s) may be inherited in a dominant fashion with incomplete penetrance(Tomson et al., 2011). It has also been noticed that synesthesia is expressed more frequently in females, the female-male ratio within families being 2: 1 indicating X-linked dominance(Ward & Simner, 2005). Subsequent analysis in larger samples show that the mode of inheritance is more complex. Data suggests that different forms of synesthesia are underlined by different genetic mechanisms. The first whole genome scan of synesthetic families was attempted by (Asher et al., 2008). Their results

demonstrated that auditory-visual synesthesia is likely to be an oligogenic disorder subject to multiple modes of inheritance and locus heterogeneity. Linkage was found to chromosomes 5q33, 6p12, and 12p12. Another research DNA collection based suggest that coloured sequence synesthesia is linked to a region on chromosome 16q(pedigree shown below)(Tomson et al., 2011). The first comparative twin study of colour sequence synesthesia found that it has a pairwise concordance of 73.9% in monozygotic twins, and a pairwise concordance of 36.4% in dizygotic twins implicating that synesthesia is substantially influenced by epigenetic and environmental factors(Bosley & Eagleman, 2015). Moreover individuals with autism spectrum disorder, savant abilities and sequence space synesthesia share some genetic variants(Bouvet et al., 2019). People who have aphantasia are also capable of being synesthetes. It has been reported that aphantics have more autistic traits along with weaker perception and imagination.(Dance et al., 2021). Though this study has little relevance to our research, it stands as an anomaly to one of our conclusions (most synesthetes are creative). Despite having a significant role in synesthetic phenomena, it can't be stated that genes are the sole determinants of the intricacies of the synesthesia experienced by an individual. Semantics and cultural exposure also play a role in the subjective experience of this phenomena making it idiosyncratic.(Mroczko-Wasowicz & Nikolić, 2014)



At this point it is necessary to get briefly acquainted with neurodegenerative disorders as the goal of our study is to integrate synesthesia in the prophylaxis and treatment of dementia.

Dementia is commonly manifested in neurodegenerative disorders like Alzheimer's, Parkinson's, Huntington's, multiple sclerosis and amyotrophic lateral sclerosis (35% of patients experience behavioural impairment, with an additional 15% having frontotemporal dementia). Certain disorders like multiple sclerosis, Huntington's and ALS due to their aetiology are a downward spiral and our suggested therapy would most probably not be of much use. But induction of synesthesia as a therapeutic procedure could have vast potential in the treatment of diseases like Alzheimer's. And the same techniques can be extrapolated with little modulations, in the treatment of Parkinson's.

Here for simplicity, we would explain the compliance of synesthetic training as a treatment methodology for dementia caused due to Alzheimer's. Aetiology behind Alzheimer's is the synaptic accumulation of beta amyloid proteins that progressively aggregate to form plaques and subsequently interfere with the neuronal communications. Microglial cells are responsible for the clearance but accumulation may occur due to increased production or decreased clearance of the amyloid proteins. In later stages of the diseases tau protein tangles also form. Risk factors

include-increasing age, cardiovascular disease, genetics (APOE gene) and disrupted sleep patterns. At the age of 40, pet scan reveals the beginning of beta amyloid aggregates. But the individual remains asymptomatic. The cascade of disease is 'tipped off' only after fifteen to twenty years of plaque accumulation. When this occurs, the microglial cells (macrophages of brain) release oxygen free radical, nitric oxide, protease and inflammatory cytokines. It is estimated that this might clear away the whole synapse itself. Tau protein tangling by mid stage Alzheimer's is marked by the beginning of neuronal death. This is when signs of decreased cognition will start appearing. The best time to intervene would be until the aggregations are small enough to not tip off the balance and most drug development strategies are aimed at creating a compound that prevents, reduces or eliminates amyloid plaque accumulation. Following a healthy lifestyle and maintaining a cognitive reserve is responsible for delaying the progression or manifestation of the disease.

"A puzzling feature of the neurobiology of Alzheimer disease (AD) is the heterogeneity of clinical outcomes in individuals with comparable degrees of pathologic lesions in the brain."(Iacono et al., 2009)

This statement is emphasizing on the astonishing observation of the 'nun study' in which 678 nuns all over the age of 75 were followed for more than two decades. They were regularly given physical check-ups and cognitive test and when they died their brains were donated for scientific research. The autopsy revealed plaques, tangles and brain shrinkage i.e., full blown pathological Alzheimer's. Despite these pathological markers, the nuns to whom the brains belonged showed no signs of dementia while they were alive. This mind boggled all the researchers. It was theorized that these nuns had a greater number of functional synapses hence higher cognitive reserve. So even if a debilitating disease like Alzheimer's compromised some of their synapses, these people are still resilient to its pathology due to recruitment of yet undamaged pathways. These extra back-up connections are created when we learn new things which are rich in meaning. These emerging connections are stronger if accompanied by the visual, acoustic or emotional activation. And connections will be quite weak the individual tries to simply retrieve the information already learnt. Therefore, solving puzzles, crosswords and sudoku will not provide significant improvement. In an average brain, there exist more than 125 trillion synapses. Moreover, the nervous system constantly undergoes the process of reorganization called neural plasticity. The key to defeating Alzheimer's lies in the activity of this process wherein neural connections and synapses are created and strengthened.

Hyperconnectivity is the basis for all theories of synesthesia and hyperplasticity always accompanies synesthesia training and induction. For us the utility of this phenomena in treatment of dementia seems infinitely transparent. We have extrapolated the research conducted in fields of synesthetic training /induction and applied slightly modified forms of these methods such that

they are congruent with the basic therapy that a patient with dementia undergoes. The detailed procedure is provided separately after the experimental survey.

Hypothesis:

-There exists a pre-establishment of connection between synesthesia and higher cognition as well as the connection between higher cognition and lower predisposition to neurodegeneration. Henceforth we infer the presence of an apparent connection between synesthesia and lower predisposition to neurodegeneration.

-Based upon the same ideology, we imply that synesthetic induction in patient with neurodegeneration will either delay the progression or may even reverse it.

Methodology:

Experiment questionnaire was created on 'google forms and formfacade' with 20 questions. It was distributed on different platforms among 100 people, Participants were mostly undergraduate students (20 to 30) while some of the participants were working (25+), while 2 of them being housewives (50+). There was also participation by 50+ age working class.

The questionnaire was arranged in a way so that their synesthetic ability and predisposition are tested in different section, 9 of the questions being synesthesia related and 11 other testing 6 neurocognitive domains and genetic and behavioural predisposition to dementia.

In the first 6 questions relating to testing synesthetic ability, 5 answers were allotted to each question where first option measured projection synesthesia, second option measured the association synesthesia while the subsequent options measured the degree of synesthesia-like capability in a descending order such that an individual choosing the last option possessed no synesthesia-like tendency. Each answer was graded 4,3,2,1,0 points to a, b, c, d, e respectively. The first three answers showed synesthetic ability in a person. Points were given to the individuals based on their answers and the summation of points were given at the end of the section.

The second section tested 6 neurocognitive domains which are:

i. Perceptual-motor function
ii. Executive function
iii. Complex attention
iv. Social cognition
v. Learning and memory
vi. Language

- In perceptual-motor function participants were asked whether they confused right and left while giving direction, or they often bumped into people or accidentally threw away a thing they were meant to keep in past 3 months.
- Executive function was tested by giving them a scenario with multiple option and participants were asked to choose one of the options that would be appropriate for the scenario, the options were graded as 4,3,2,1,0 to a, b, c, d, e respectively.
- Complex attention was tested by asking participants whether they often forget things when they enter the room or do, they lose things often; checking their sustained, divided and selective attention.
- To check social cognition a picture was given for participants to recognize emotion the picture is depicting.
- In the beginning of the form participants were asked to memorize certain words in order and after few questions they were asked to select answer that matches to the words that they have memorized.
- For language participants were asked to find antonym of a given word. Although this question is insufficient to analyse the linguistic competence of an individual but excess number of questions would discourage the participants.
  In this section itself we assess the genetic and behavioural predisposition to dementia and integrate these scores with cognition.
  From questions 10 to 15 the marks were allotted in the order of 4,3,2,1,0 to options a, b, c, d, e.
  From 16 to 20 the question was one word answer and 4 marks were given to correct answer and other options were marked as 0.
  After each section total points were calculated and their synesthetic ability and predisposition to neurodegeneration were compared.

Questionnaire- (explained above, read only if felt necessary)

SYNESTHESIA
Imagine being able to watch an aurora while listening to your favourite acoustic without ever visiting the north pole. It is possible for some people! they are called synesthetes. Take the quiz given below to find out if you are one of them. Plus, we are also testing your cognitive abilities and will give you personalized feedback if you ask for it. BUT IT IS EXTREMELY IMPORTANT FOR OUR RESEARCH THAT YOU ANSWER HONESTLY. We will keep your responses confidential so you don't have to worry about its settings
Age

15-20 (4pts)
21-30(3pts)
31-40(2pts)
40-50(1pts)
50 above(0pts)
Remember this in order as it would be asked in later question to test memory, please be honest with your answer: eats, bitsy, bites, busts, drain.

1. Do you associate colors to plain black letters or numbers
• I've not seen colors over the text but I can immediately think of a linked color when I see particular letter or number (4ts)
I see colors over the text inside my mind's eye (3pts)
• I've not seen color over the text but if I absolutely had to then I will be able to link a suitable color for letter or number (2pts)
• I've never experienced this neither will I be able to link any color to any number (1pts)
• I see color project out on paper over the letter(0pts)
2. Do you see colors when you hear music?
• Yes, I see inside my mind's eye
• Yes, colors are associated with particular chords (for eg: o is yellow) and I see it projecting out of my head
• No, but I can link a color to whole piece of music based upon its mood if I think hard enough
• This idea seems alien, I can't relate color with sounds
• No, I don't see colors when I hear music But I can quickly link color to the particular note such that I might be able to paint and also track picture representing the music

3. Can you observe timeline (Days/weeks/months) as visual patterns around you? *settings
• Yes, it aids memory about events of the past each (Day/month/year) takes a specific shape right before my eyes, I'm good at history because I can remember dates
• Yes, each (Day/month/year) has specific section in my head & helps to remember past events& organizing and planning for future events
• No, but if I think about timeline as a spatial phenomenon then I can say that I'm facing the future and my back is towards the past (opposite depending upon your culture)
• No, but I will be able to draw timeline on paper with my birth being on the left side of paper and my present on being on the right end (opposite depending upon culture eg: Arabic people will have birth on the right side)
• I cannot relate to any of the above.

4. Does mental map of numbers appears whenever you think about numbers?

- Yes, each number has a distinct location
- Yes, but it's more like a mental image and doesn't project on my visual view
- No, but I have been faster at Identifying mathematical pattern or which out of two number is greater as compared to my peers
  No, but I can imagine a number line mentally for any given set of consecutive numbers
- I don't relate to any of the above

5. Have you ever associated particular gender/age/personality to numbers or letters

• Yes, it has always been that way, At least the numbers from 1 to 10 have distinct personalities and quirks (eg: 5 is an introverted girl, 1 is actually a 4-year-old boy)

• Yes, not all numbers or letters have specific traits but certain numbers do hold particular characteristics in my perception.

• No, but if I think about it long enough then I will be able to assign some gender roles to the numbers or age to the letters

• No, I can't but this seems like an interesting phenomenon

• no, associating Identities to numbers seems part of mysticism not science

6. First time you meet someone and then meet the same person the second time, how do you usually recognize them or their names, have you ever associated any of the following in order to remember them?

- I usually remember them by color of their eye, smell, color of the dress they were wearing for the first time, tone of their voice, facial expression or features
- I'm just good at memorizing names, but sometimes physical features do matter
- I'm not good at remembering names even though I remember their faces
- I can remember names only if I try very hard
- I can't remember people I met once

7. If you ever had to relate heavy and light to day or night, what do you feel?

- Day seems heavier to me & Night seems lighter to me
- Night seems heavier to me & Day seems lighter to me
- They both seem heavy equally or light equally
- I might consider it now
- never thought about it

8. Have you ever hated someone just because of the way their voice sounds for no apparent reason

- yes

- yes, but I try to ignore that instinct and give the person a fresh start
- yes, but not every person I meet
- No, but I can understand how this might work
- No that is so absurd

9. Have you ever associated someone's mood as warm or colder.

- Yes, happy mood always seems warmer to me while the bad or negative emotions always seemed colder to me
- Yes, happy mood seems cooler to me while the bad or negative emotions seemed warmer to me
- No, I never associated based on the temperature but If I think carefully enough it makes sense to me
- Not really, I can't relate to any of it
- This is stupid

COGNITION

10 How often any of the mistakes happened to you in past 3 months. Do you read something and find you haven't been thinking about it and must read it again, do you find you forget why you went from one part of the house to the other, Do you fail to listen to people's names when you are meeting them, Do you fail to hear people speaking to you when you are doing something else

- never (4pts)
- rarely (3pts)
- occasionally(2pts)
- quite often(1pts)
- very often (0pts)

11. Have you experienced any of these in past 3 months? Do you find you confuse right and left when giving directions, do you bump into people, do you fail to see what you want in a supermarket (although it's right there), Do you find you accidentally throw away the thing you want and keep what you meant to throw away – as in the example of throwing away the matchbox and putting the used match in your pocket, do you drop things?

- none
- some of these rarely
  some of these occasionally

- at least three of these
- all of these

12.Do you sleep walk?

- I don't sleep walk or talk, I have sound sleep
- I sleep talk rarely, I just mumble
- no but I sleep talk, I howl and cry and don't wake up unless someone wakes me up
- yes, but rarely
- yes, quite frequently

13. Does someone in your family have dementia (it could be mild for example mixing up names, frequently forgetting things here and there) *settings

- NO
- Far off relative
- Maybe, I'm not sure
- yes, but very mild form of dementia
- yes, immediate relative

14. You see boy getting stabbed on the way to your work and there's no on there apart from you, the victim seems in critical condition and probably might die if he doesn't receive any help, culprit runs away after last strike, what would you do? Imagine you have some medical experience.

- Call for emergency first and wait till the help arrives, not approach victim since culprit might still be around and you could endanger yourself
- Storm towards the boy and give him first aid and call for emergency, possibility of culprit coming back to crime scene must be less since he must be afraid the police might have arrived
- Not intervene in anyway.

- Chase the culprit.
- I don't know what to do.

15. Can you quote 6 phrases from a speech/poem/novel/movies/t.v shows in the next 30 sec

- Yes, easily
- yes, with some effort and adrenalin
- yes, but I need more time
- maybe
- no

16.Grief is opposite of

- Desolation (0pts)
- Exhilaration(4pts)
- Anguish (0pts)
- Bereavement (0pts)
- Sorrow (0pts)

17. Do you remember the order of the words that was mentioned at starting of this form if yes click on the correct option

• Bitsy, eats, busts, drain, bites (0pts)
• Eats, bitsy, bites, busts, drain (4pts)
• Eats, bites, busts, bitsy, drain(0pts)
• Bites, eat, bitsy, drain, busts (0pts)

18. Assumptions: All Army officer have served for at least 5 years. No army officers are addicted to drugs. Some army officers are vegetarians. Conclusion: Bob, a former army officer is both vegetarian and have served for exactly 4 years If the assumption is true, is the conclusion:

- correct (0pts)
- Incorrect (4pts)
- cannot be determined based on information (0pts)

19.What emotion is this

- Anger, I’m about to beat this witch (0pts)
- confused (you guys are getting paid?) (4pts)
- Happy (world is rainbows and colors) (0pts)
- disgust (what is she wearing) (0pts)

20. If songs on music app is 3$ per half dozen, how much would it cost to buy 24 songs?

- 6$ (0pts)
- 12$ (4pts)
- 9$ (0 pts)
- 18$ (0 pts)
- 24$ (0 pts)

Results:

After comparing the points of each of the 100 participants, we calculated mean average of all the points of both synesthesia and cognition, synesthesia’s average point being = 24.18 and cognitions average points being = 14

70 of the participants showed lower than average synesthesia like ability. This may be attributed to the high disparity in synesthesia scores and less understanding of the questions among the participants. While one of the participants showed cognition below than that of average, which may be attributed to less disparity in scores and easy questions. Rest of the partakers showed proportionate results.

We extracted 18 out of 100 participants showing remarkable comparison between their synesthetic and cognitive capability which supports our theory, while some showed higher value than the other in comparison, creating an anomaly for our hypothesis.

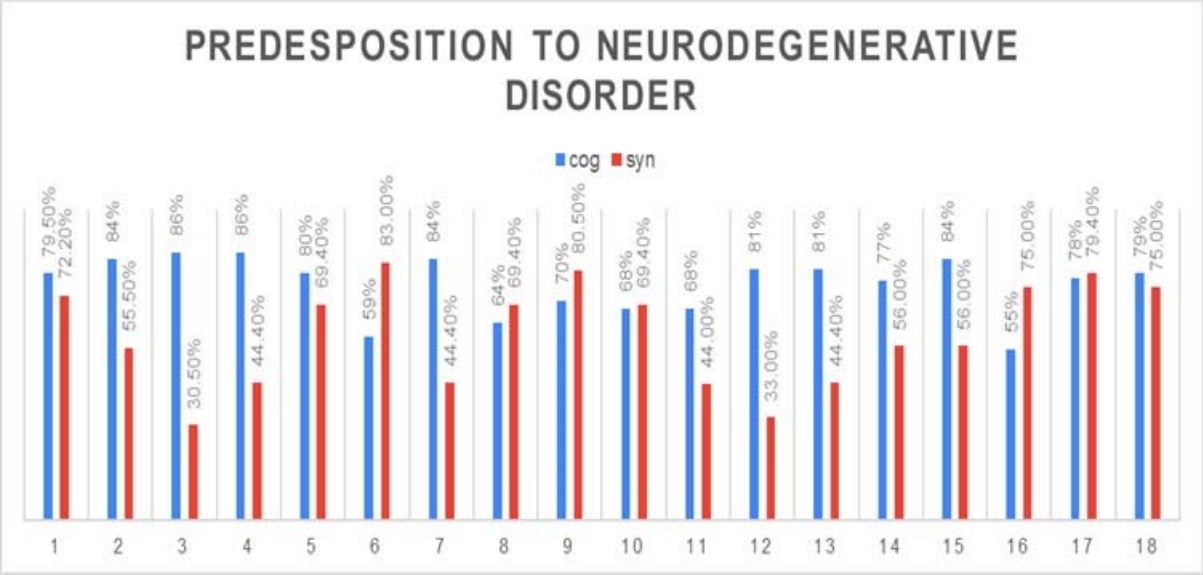


fig (1.1)

Participant 1, 5, 8, 9, 10, 17, 18 showed steady comparison between cognition and synesthesia, remaining participants showed one value higher than the other. These results help us to compare how synesthesia is proportionate to cognition, helping us to integrate our work to prove our theory. The increased disparity between cognition and synesthesia in few of participants is justified in the 'Discussion' part of our paper.

Limitations:

-With regards to survey form-

-Most of the participants were unaware about synesthesia. This concept being alien to the general population, made the questions a bit difficult to understand.

-Even though it was mentioned at the beginning of the form, many of the participants jumped straight to the questions and omitted the training of recall question (eats, bitsy, bites, busts, drain).

-The most common feedback we received was that the questions were too lengthy so were the answers, some participants tried to fill the form as an obligation without focusing on the sole purpose. We asked participants if they had to focus more on the questionnaire would their answers be different from what they had chosen previously and their answers were "yes", showing that some participants were uninterested or callous. This agreement also justifies the disparity between scores of synesthesia (being too low) and cognition (being too high).

-Each neurocognitive domain question was present to test every 6 domains but yet the cognitive questions were too basic and were not time bound to understand individuals time management & problem-solving skills. This again justifies the comparatively high scores in cognition.

-manual explanation of questions occurred for only about 30 participants.

-Even after searching for confirmed synesthetes and reaching out to them, we didn't receive a response. Our results are based on people who show synesthesia-like capacity.

Discussion:

As per the results of our experimental design there are many holes to fill. People showed high disparity in synesthesia and cognition. Some showed higher cognition with quite low synesthesia. We interviewed these people to understand what made them score less in synesthesia and the most common answers were that the form was too lengthy or they didn't pay much attention to the question. If they had to fill the form again there's possibility their answers would be different leading for their scores to differ at the same time and hence synesthetic scores would be comparable to cognitive scores resulting in the data aligning with our hypothesis.

-approximately 30 of the participants who worked under our supervision had convincing result their synesthetic association and cognitive ability were tested fairly and had steady results in both comparisons.

-In the section of cognition only one person had received points lower than the average set points as the questions were too basic also age factor was not included in the cognitive section while age factor was included in the section where synesthetic potentiality was being tested.

-It is our shortcoming for not including age factor whilst calculating cognitive function, but it is legitimate to include age factor in the section for synesthesia as the when age increases synesthetic capabilities decreases(Simner et al., 2017) which leaves us to question is decreasing synesthesia one of the contributory aetiology behind decreasing cognition with age?

The 18 participants who scored highest in both the domains out of the 100 participants show the following variability- Participant 1, 5, 8, 9, 10, 17, 18 showing steady results in both the aspect had no genetic or behavioural predisposition of dementia which supports our theory of people who have synesthetic associated capability have lesser predisposition of dementia whilst the remaining participants show limitations to our experiment due to less comprehensible questions.

-Individuals who showed higher synesthesia associated capabilities seemed to be skilled at arts, paintings and poems just as individuals who showed higher cognition seemed to be good at science, General knowledge, maths etc. It's not fair to assume that people who have higher

cognition can't be good in writing poems or arts just as it is not fair to assume that people who are good in arts can't be good at solving math problems these skills are acquirable, but some skills do come naturally to us and it is up to us to decide which set of skills we want to practice more and our results show nothing more than that, one of the participant is a youtuber and she chooses to improve her art skills than one participant who is medical student who chooses to improve his cognitive skills. Anyhow learning any set of new skills helps in formation of neuronal connection and our results show synesthetic ability are associated with higher cognition.

-It may seem like we are justifying excessively in order to prove our hypothesis, but with better experimental design including a smaller sample size and manual explanation of questions to participants, we are positive that the hypothesis will stand true.

Experimental therapeutic design:

Here we have referenced from two studies involved in induction(Nair & Brang, 2019) and training of synesthesia (Bor et al., 2014). Modifications were inserted into these test designs to create friendlier versions of these procedures for patients with dementia. As these patients usually do not have the patience to go through elaborate settings and timetables.

The first study includes synesthetic training of Grapheme-colour synesthesia:

In the original study, non-synesthetic underwent extensive training to reinforce 13 specific colour-letter associations through a course of 9 weeks with 30 minutes training period each day.

In our modified experiment, we train the patients with dementia by asking them to associate 3 letters (example-A, B, C) to a colour of their choice. For instance, A is yellow, B is green, C is red. Then we ask them to memorize it. The

Subsequently, we project 3 coloured numbers on the screen, ask them to memorize the association. It should be noted that there shouldn't exist any congruence amongst the colours presented. Moreover, the time associated with this training session is flexible and in accordance with the patient's limits of exertion.

The second test involves inducing chromesthesia:

In original test participants were asked to remember the curves, symmetry, horizontal lines and triangles in arial black letters(A-Z). then they were situated in a stimulatory environment involving a pitch-dark room with 2 speakers on either side of the patient. They were asked to visualize the arial black letters via auditory input from the speakers. Beeps were emitted at regular intervals inducing synesthesia. The goal was that the test subject should be engaged in

extensive visualization if imagery while he/she hears the beeps. This way the individual unknowingly makes association between the sound and visual perception.

We created a friendlier version; the patient would be asked to get some exposure of the outside environment for instance to a park for some time. After returning home we would start the procedure by asking the patient to cover their eyes (aided by the care giver) such that light is completely blocked from vision. This may stir up the patient but the caretaker needs to console him/her. In a dim lit room with his/her care-giver around so he/she feels safe, we would ask the patient to visualize and draw with the blindfold on whatever he/she saw in the park. The caretaker would be simultaneously checking the authenticity of the drawings and also be helping the patient with recollection. The process of visualization and drawing should occur in silence while the patient is wearing headphones such that beeps can be heard at regular intervals by the patient. Again, there ought to be retention of flexibility of time period in this exercise as well such that the patient doesn't go through any kind of inconvenience.

We would combine these two tests together and induce the synesthetic mechanisms.

We would first ask patients to memorize letters with their given number and ask him to take a stroll in the park/museum/zoo etc. (any place that fascinates the patient), while he/she is taking stroll, the care taker would point at an object and ask the patient which colour the object is and what letter is it associated with. In this patient, three aspects of management of dementia are being covered, taking stroll in park is making him exercise, care taker pointing at an object and asking him/her questions about colour association is making him/her practice grapheme-induced synesthesia and simultaneously making him aware about surroundings which would be helpful with inducing chromesthesia. In induction of chromesthesia patient is given free space where he can visualize things which helps patients with recalling visual memory.

This experiment can be performed by giving patients different letters and tasks ever week for next 6 months (as opposed to original 9-week period in healthy non synesthetes) and test whether their cognitive ability has improved or not. It is important here to note that even if synesthesia is not induced or apparent (increased activity in parietal cortex) still the experimental treatment would be considered a success if the patient shows signs of improved cognition attributed to the synesthetic induction.

There prevails a unique balance between set routine and trying out new things when it comes to the proper management of dementia. The routine is important since it helps the patient retain certain skills by the application of 'use it or lose it' principle. Hence if the patient has a particular time to get up, practice synesthetic training and get dressed to go out for a walk then patient is also bound to feel more in control and confident. On the other hand, new experiences are important for increasing plasticity. The time period during which the patient is out of the house is a crucial aspect of the experimental design. First and foremost, the patient receives aerobic

exercise which is a supplementary treatment. Moreover, the patient may interact with new people and it is advisable to take patient to new places every day on a weekly rotation basis. So, this will help with the neural plasticity. Almost as important is the role of the caregiver who is accompanying to patient. While being exposed to the outside world it is the job of the caregiver to maintain the alertness of the patient and keep them engaged in the cognitive exercise of observing, recognizing, recalling and registering. Simultaneously making the process fun and less stressful.

Limitations with regard to therapeutic experimental procedure:

-Synesthetes do not show significant difference in long term memory when compared to general population. Although their visual perception and short-term memory are enhanced. Dementia patients demonstrate a loss in long term memory as well so how is the induction of synesthesia in such patients going to help in this regard? (answered in 'Discussion')

- Another challenge which arises is to find different place the patient can take a stroll to each day to break monotony.

- Inducing synesthesia in people suffering from dementia comes with great limitations as we will be dealing with patient who are unwilling to participate in experiment, they might get confused and scared, they might become moody and suspicious of everything that would be hard to deal with.

-Management of behaviour in patients is difficult as to what would work today for them might not work tomorrow or not work at all.

Discussion with regards to experimental therapeutic procedure:

Even though inducing synesthesia in people showing signs of dementia aids only short-term memory and not long-term memory, still inducing synesthesia in people with dementia will improve hyper plasticity of neurons creating synaptic changes at the end of dendrites which happens in response learning and memory formation. So even if only short-term memory (excluding long term memory) is being enhanced, it is still improving the cognition.

It won't be possible to get actual result unless there are two groups, one group in which we have induced synesthesia and one control group in which we have not, we need to compare these two groups to see whether this experiment has worked or not.

Conclusion:

The experimental survey proved the hypothesis that with increased synesthesia-like tendency the predisposition to neurodegeneration decreases.

In prospective studies survey can be modified to measure the neurodegeneration of the general population with higher sensitivity and at a larger scale.

Our results show that if synesthetic induction in patients with dementia occurs then there is high probability of this procedure to increase quality of life of the patients.

We have restricted our experimental therapy procedure to include only induction of chromesthesia and training of grapheme colour synesthesia as these two modalities have the evidence of being successful methods of acquiring synesthesia. But we present induction in dementia by different methods and experimental designs as a topic with scope of research. Prospective research in this domain could include induction of other kinds of synesthesia with reduced capital investment in the overall procedure. Also including the synesthetic regime in training programs of nurses and care givers if this method is widely accepted as a treatment modality.

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Psychological impact of covid19 pandemic on medical student

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Abstract- Corona virus pandemic started in china and spread very rapidly all over the world. It causes psychological impact on most of the humans but medical students were mostly affected. Our aim was to identify psychological problem and the reasons affecting psychological health of students. It causes depression, anxiety, stress in medical students due to various reasons like financial problem, quarantine, online education, due to covid19 infection in family member. We did quantitively research by online questionaries among students from different medical universities in the world. We got 140 responses among them most of the students are from age 18-21 and their nationality is Indian. The 64.2% students are from Georgian American university. The 50% students feel stress due to covid19. Most of the students live with friends and they are very concerned about their family. Highest number of students faced financial crisis due to covid19 and they are very concerned about their studies because of educational quality got affected due to online education. Students didn't get enough practical knowledge. 48.6% students are afraid of getting covid19 infection and 62.9 % students are living with their friends. We conclude that students who faced financial problems, quarantine problem, educational problem, family health problem has more depression, anxiety and stress.

Keywords – covid-19, anxiety, depression, medical students

Objective- Our aim was to study how covid19 affected psychological health of medical students. What factors affected student's health? Are they feeling any anxiety, depression, stress due to covid19 and what factors triggered these? Also, student's family have economic problem due to lockdown. How this affected their psychological health. Some international medical students travel to their home country during pandemic these cost lots of money in quarantine and causes many problems. How these factors affected their health? Due to covid19 many medical students have to attend the classes online and it affected their studies and it decreased the quality of the medical education. We aimed to learn effects of online education on the anxiety and depression of the medical students.

Introduction - Corona virus pandemic started in china and WHO declared global emergency because of covid19 causes a lots of death in the world. This pandemic causes emotional and psychological disturbance in people of both developing and developed countries. This virus originated in china and spread to the world very rapidly through human-to-human transmission **(H. Sulaiman, M. Sleman 2020).** Now there is vaccine available for covid19 but we have restriction to keep vaccine in low temperature, we have limited number of vaccines. Still, it will

take 1-2 years to distribute vaccine in the whole world. Many countries gave priority to healthcare workers and old peoples for vaccination.

The continuous spread of the epidemic, strict isolation measures and delays in starting colleges and universities across the world is expected to influence the mental health of medical students. There have been reports on the psychological impact of the epidemic on the medical student, patients, medical staff **(Q. Chen et al., 2020; Yang et al., 2020; Li et al., 2020)**. Due to the pandemic that forced educational institutions to eliminate in-person teaching sessions, medical students needed to adapt to new educational environments, such as distance or remote e-learning **(Al-Balas M, Al-Balas HI, Jaber HM, Obeidat K, Al-Balas H).** Many of the things in medical education are supposed to be practical and because of the social distancing and the lockdown, medical students were not able to gather practical knowledge and they only got the theoretical knowledge. Because of this many students are afraid to conduct the practical examination and working in the hospitals. The prevalence of anxiety among medical student was estimated 33.8% before covid19 pandemic and Also, a meta-analysis done in 2016 showed that depression was prevalent in 28.0% of medical students globally. **(Quek TTC, Tam WWS, Tran BX, Zhang M).**

Georgia has different international medical universities. There are many international and local medical students are studying in Georgia. In early march, Georgia suspended flights for different countries, and because of a declaration of situation the closure of schools and universities, including medical universities took place. **(Makhashvili N, Jana Darejan Javakhishvili)** So many international students stuck in Georgia. Initially they faced shortage of resources like mask, sanitizer and groceries. These things caused fear among students and leads to anxiety and depression. Same problem is faced by international students in countries like Russia, Philippines, Armenia, Turkey and India.

Method

Study design – We perform cross sectional quantitative study process. We performed cross sectional study on 140 medical students from different countries. Most of the students from Georgian American university of country Georgia.

Setting – We have created questionnaire form in the google forms. We distributed this questionnaire to medical students in different countries through WhatsApp, Gmail, Instagram, telegram, Facebook. Most of the questions were mandatory in survey. Survey is done in 8 days.

Study subjects- The 140 students were chosen by simple random technique. These includes students from different countries with different race, ethnicity and age. This survey includes question related to their gender, nationality, university and country, year of studying, depression and anxiety feeling among scale of 0-10, residential status, stress, fear related to covid19,

concern of family health status of students and family, financial problem, online education and travel to home.

Statistical analysis – Data analysis is done by excel tool. Basic descriptive statistics were computed for all variables and reported as number of cases (frequency) and percentage for categorical variables and means and standard deviation (SD) or medians as appropriate for continuous variables. Average of depression and anxiety as well as corelation of different parameters with anxiety and depression is done by excel.

Hypothesis – Covid19 pandemic causes psychological problems like anxiety, depression, stress among medical students. The factors like travelling to home, financial crisis, online education, covid19 infection in family increases the psychological problems.

Results – We analysed that 67.9 % respondents were from age 18-21 ,27.1%from age 22-25 years and 5% students are more than 26 years. As we consider gender 50.7% respondents were male, 46.4 % respondents were female ,1.4% others and 1.4% students were not prefer to told their gender. 88.6% students responded that they belongs to Indian nationality while 11.4% belongs to other countries. 64.2 % student responded that they are study in Georgian American university, 12.8% in MUHS,22.8% students in other universities. 2.9% students were from 1st year ,24.5% from 2nd year, 34.5% from 3rd year ,12.9% from 4th year ,2.9 % from 5th year.

In case of stress 50% respondents that they were stressed due to covid-19, 23.6% didn't feel any stress and 26.4% students weren't sure about the stress. 75% students from 1st year responded that they feel stress due to covid-19, and the remaining 25% responded they weren't sure. In case of 2nd year Students 47.05% students responded as they feel stress, 26.4% responded they didn't feel any kind of stress, where as 26.4% weren't sure. Among the 3rd year students 44.7% students feel stress due to covid-19 where as 26.3% didn't feel any stress due to pandemic and 28.9% weren't sure about stress. Among 4th year students 66.8% students responded as they feel stress due to covid19 while 16.6% students didn't feel any stress due to pandemic and 16.6% weren't sure about stress in 5th year students, we observed that 75% students felt stress and 25% didn't feel any stress Average depression out of 10 due to covid19 pandemic among 1st year student is 7, 2nd year student is 4.44, 3rd year student is 5.61 ,4th year 6.11 ,5th year 8.25. Average anxiety out of 10 in 1st year students is 8,2nd year students 4.41, 3rd year student 5.32 ,4th year student 6.05, 5th year student 8.5 So depression and anxiety are highest in 1st and 5th year students.

In case of residency 62.9% student lived with friends during pandemic,22.9%with family, 11.4% lived alone and 2.9% students lived with other members.46,4% respondents family got infection with corona virus ,44.3% respondents' family not infected with corona and 9.3% respondents are not sure about infection. 80.7 % respondents feel very concerned for their family 17.9% feel somewhat concerned and 1.4% respondents were not concerned about their family. 48.6% students among respondents were afraid of getting covid19 30.7% weren't afraid of getting

covid19 infection and 20.7% students were not sure. Many students face financial problems due to loss of job of their parents. 57.1% students said yes that they faced financial problem, 27.9% students said they didn't face any financial problems and 15% students were not sure about financial problem.

65% students were concerned about their studies due to shifted toward online education, 22.1 % didn't concerned and 12.9% weren't sure. As we asked reason of concern about shift toward online education 51.4% students agreed that online education is not effective as onsite education ,53.6% agreed that due to online education they had less clinical practice. 24.3%students had fear of sudden changes in curriculum and 10.7% students were concerned due to other reasons. 60% students responded that they travel to home during covid19 pandemic and 40% students didn't travel. We asked about depression due to quarantine and other problem. 56.1% students said yes that they feel depression, 23.7% said no and 20.1% were not sure about depression.

Discussion - In our study found that stress among male students is more than female students but in previous studies female students have more stress than male students. Studies have suggested that public health emergencies can have many psychological effects on university students, which can be expressed as anxiety, fear, and worry, among others **(Mei et al., 2011)**. Same results found in our case that students who faced lockdown, quarantine problems have more average anxiety and depression. the significant shortage of masks and disinfectants, the overwhelming and sensational news headlines, and erroneous news reports have also added to anxiety and fear **(Ayittey et al., 2020).** The stability of family income also was a significant factor in students' experienced anxiety during the COVID-19 crisis, which could be explained by increased psychological and economic pressure **(Liu, 2013).**

65% of those concerned about the shift toward online education thought online education was less effective than in-person education. While previous studies have reported the utility and noninferiority of online learning compared to offline in-person learning **(Pei L, Wu H).** 5th year students felt more stress because some of them are frontline workers in covid wards and they loss too much their practical skills. Also 1st year students are afraid because they have no any idea about medical education and they even didn't see their university due to online classes. Most of the students are very concern about their family because they are studying in different countries apart from their families. Most of the international students travel to their home country. They faced quarantine and economical problem which leads to anxiety and depression among them.

Conclusion – We found positive results for our hypothesis Covid19 pandemic causes psychological problem like anxiety, depression and stress among medical students. Result found that male students feel more stress than female students. 5th year and 1st year medical students felt most stress as compared to other students. Average Anxiety and depression are higher among students who faced financial crisis as compared to student who didn't face financial crisis. The

anxiety, depression and stress are higher among students who are more concerned due to shift toward online education. Students who faced quarantine and other problem have more depression and anxiety. Those students who are afraid of getting covid19 showed high level of anxiety, depression and stress. Students who lived with friends has less anxiety and depression has compared to students who lived alone and with family. Those students whose family got infected with covid19 felt more stress as compare to other students.

Recommendation – We recommend all the medical student to do exercise, meditation and yoga because most of the researcher found positive effect on anxiety and depression. Yoga and meditation will increase student's concentration power and because of these they won't feel any concentration problem in online education. They should sleep properly. Students should share their thoughts and problems with anyone like friends, family because loneliness triggers depression.

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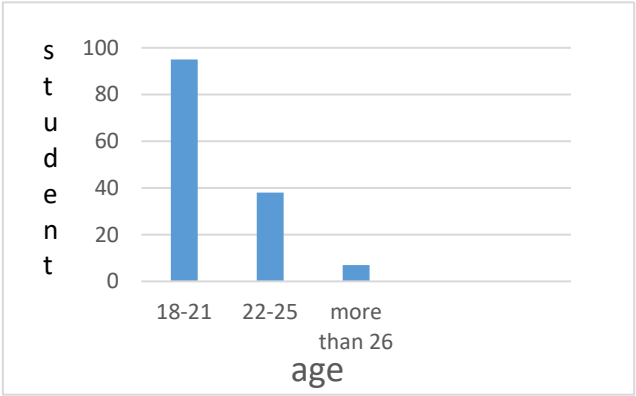
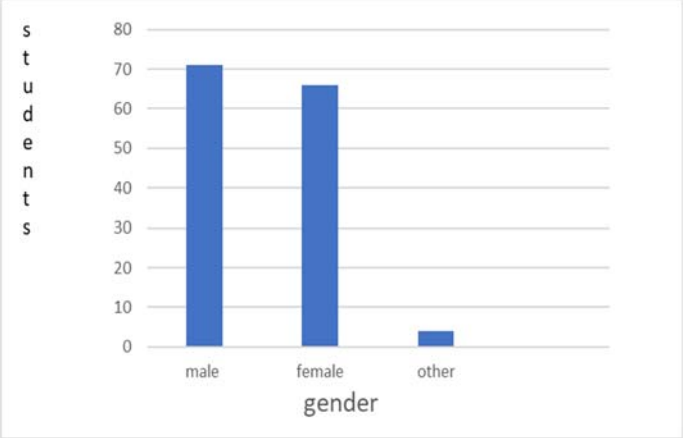
Annexure 1

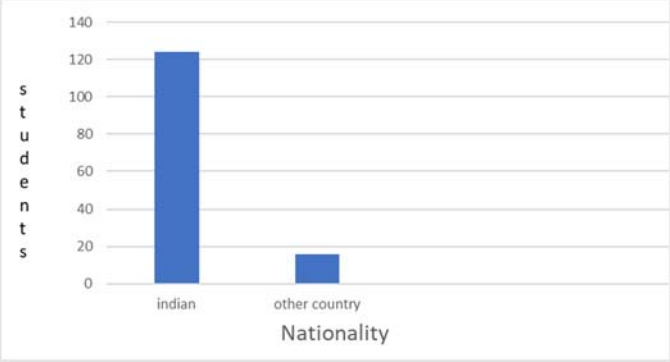
age	students
18-21	95
22-25	38
more than 26	7



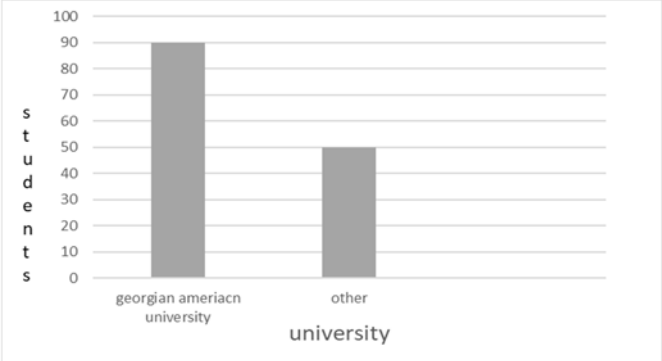
gender	students
male	71
female	66
other	4



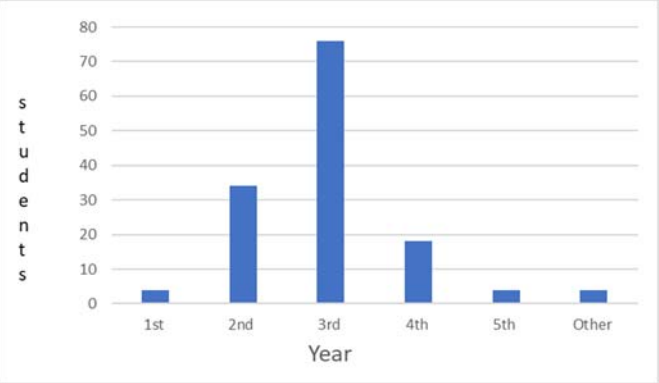
Nationality	students
indian	124
other country	16



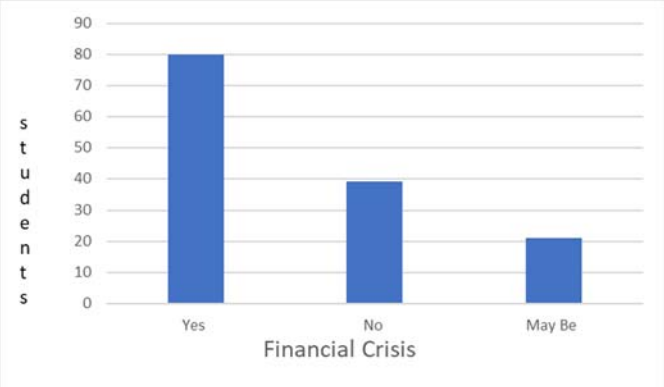
university			students
georgian ameriacn university			90
other			50



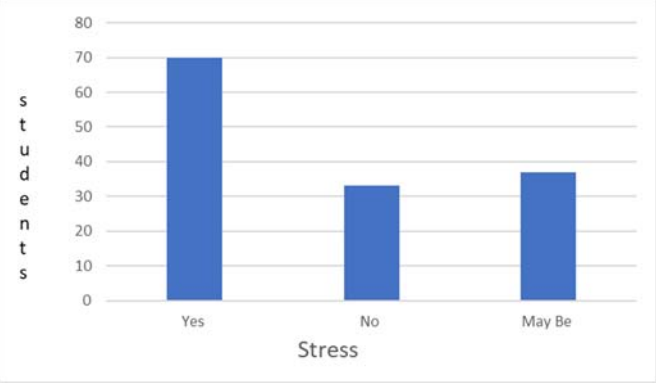
Year	Students
1st	4
2nd	34
3rd	76
4th	18
5th	4
Other	4



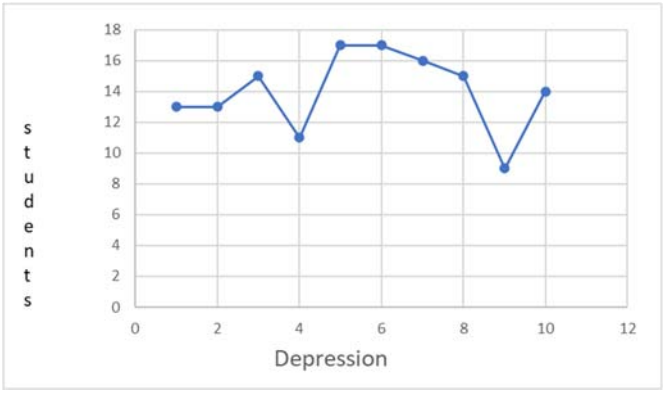
Financial Crisis	Students
Yes	80
No	39
May Be	21



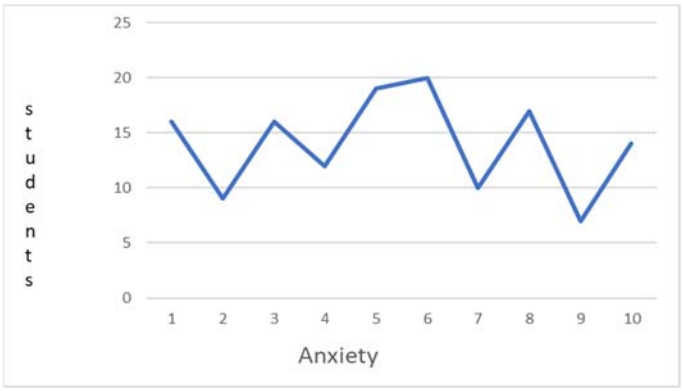
Stress	No. of Students
Yes	70
No	33
May Be	37



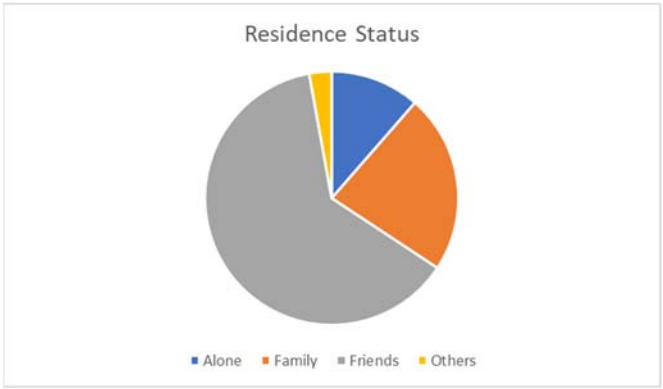
Depression	No. of Students
1	13
2	13
3	15
4	11
5	17
6	17
7	16
8	15
9	9
10	14



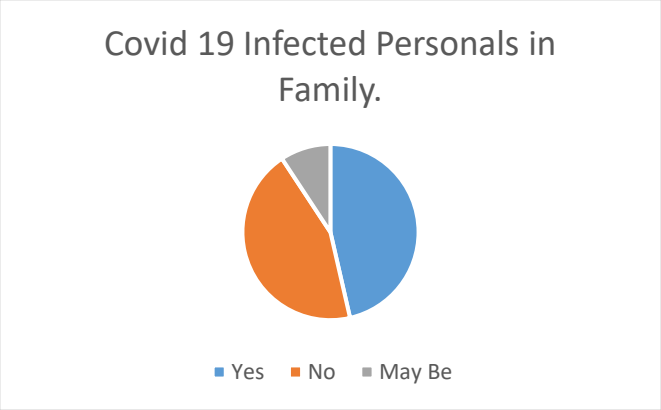
Anxiety	No. of Students
1	16
2	9
3	16
4	12
5	19
6	20
7	10
8	17
9	7
10	14



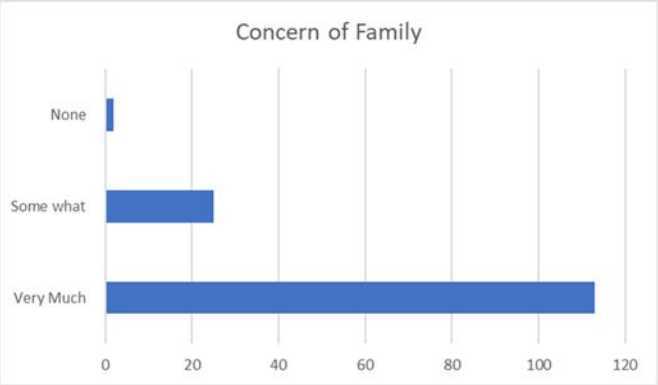
Residence Status	No. of Students
Alone	16
Family	32
Friends	88
Others	4



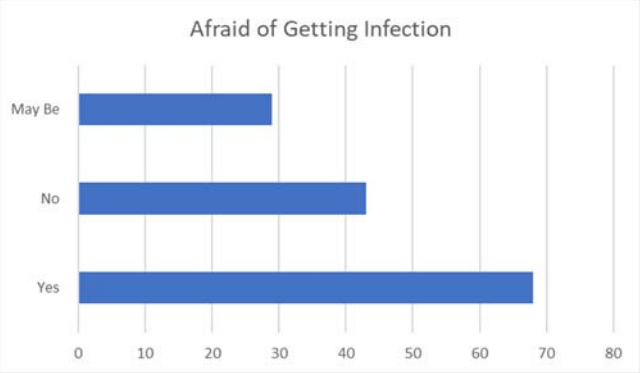
Infected in Family.	No. of Students
Yes	65
No	62
May Be	13



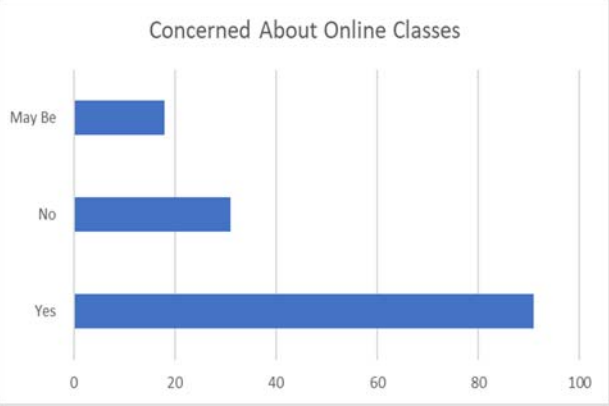
Concern of Family	No. of Students
Very Much	113
Some what	25
None	2



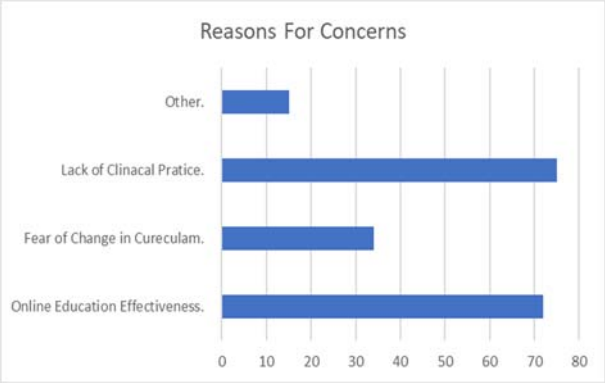
Afraid of Getting Infection	No. of Students
Yes	68
No	43
May Be	29



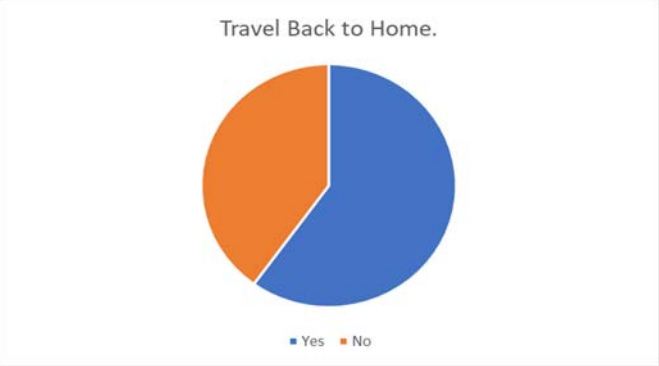
Concerned About Online Classes	No. of Students
Yes	91
No	31
May Be	18



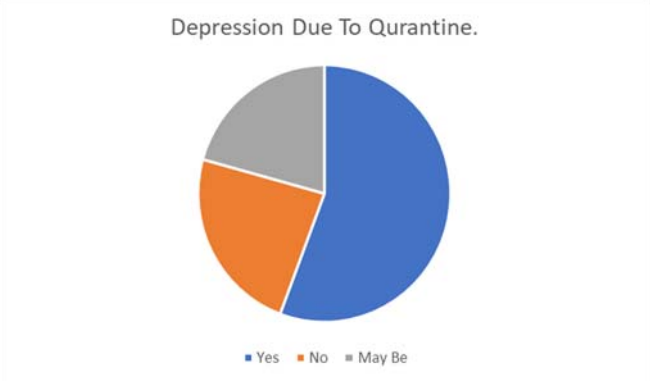
Reasons For Concerns	No. of Students
Online Education Effectiveness.	72
Fear of Change in Cureculam.	34
Lack of Clinacal Pratice.	75
Other.	15



Travel Back to Home.	No. of Students
Yes	84
No	56



Depression Due To Qurantine and	No. of Students
Yes	78
No	33
May Be	29



Annexure 2

- Age

  18-21 years

  22-25 years

  26-29 years

More than 29 years

- Gender

  Male

  Female

  Prefer not to tell

  Other

- Nationality

- Which medical university and country do you study?

- In which year you are studying?

  1st

  2nd

  3rd

  4th

  5th

none of the above

- How much depression do you feel due to covid19 pandemic as 1 be the minimum and 10 will be the maximum level of depression?

1,2,3,4,5,6,7,8,9,10

- How much anxiety do you feel due to covid19 pandemic (1- minimum, 10- maximum)?

  1,2,3,4,5,6,7,8,9,10

- Do you feel stress due to covid19?

  Yes

  No

  Maybe

- Who do you live with?

  alone

  with family

  with friends

  other

- Do your family or relatives got infected with covid19?

  Yes

  No

  Maybe/ I'm not sure.

- How much concern do you feel about the health status of your family/relatives

  Very concerned

  Somewhat concerned

  Not concerned

- Are you afraid of getting covid19 infection?

  Yes

  No

  Maybe/ I'm not sure.

- Did you face financial crisis during covid19 pandemic?

  Yes

  No

  Maybe/ I'm not sure.

- Are you concerned about shift toward online education?

  Yes

  No

  Maybe/ I'm not sure.

- What is the reason for concern about a shift toward online education?

  Online education may not be as effective as on-site education

  Fear of sudden change in the curriculum

  Less clinical practice

  other

- Did you travel to your home during covid19 pandemic?

  Yes

  No

- Do you feel depression due to quarantine and other problems?

  Yes

  No

  May be/I'm not sure.

Dissecting Barriers to Accessing Health Care in Georgia: Perspectives of Young Cancer Patients and Their Careers

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Educational program: MD Program

Abstract

The vast majority of the population today has elementary information about cancer, due to the fact that the surface level part of this matter is often talked about. But there are other important issues that need to be addressed to raise public awareness. In Georgia, which is a developing country, a lot is being done to improve their situation nowadays. However, there still is an alarming number of obstacles that children with cancer have to overcome in order to access healthcare. These matters need to be addressed as soon as possible, otherwise, an already constrained situation is bound to worsen over time.

The aim of this research is to describe the current situation of children with cancer in Georgia, also, to identify the problems that these children and their carers face. The present research is based on the interviews conducted with one of the founders of the "Monk Andrew's foundation's", 2 doctors, and 8 parents of children with cancer. The main theme was identified as: "What is the state of children with cancer in Georgia today, what struggles do they face and how can we provide aid?". There are four main factors that reflect the main theme: (1)"Monk Andrew's Foundation for Kids with Cancer"; (2)pandemic and related problems; (3) Using the method of "freezing of eggs and sperm" as a fertility preservation approach; (4) Emotional and psychosocial well-being of children with cancer and their parents.

The collected data showcased the vital importance the "Monk Andrew foundation" holds, as well as providing evidence of a great negative impact of the Covid Pandemic on children with cancer and their families. Due to the economic crisis, the crucial support that "Monk Andrew's Foundation" provided was no longer available to everyone in need. The study also showed the significance of raising public awareness among children with cancer and the "Monk Andrew foundation", since nowadays a lot of children that have been diagnosed with cancer are being treated abroad because of the parents' scepticism of the medical science level in Georgia. Also, the fund needs financial support, that's why the most important is raising public awareness. The study further describes what issues patients come upon when they want to store sperm and eggs. We also discussed the necessity of retraining doctors, which will significantly improve the psycho-emotional state of cancer patients and their close relatives.

The prime goal of my research is to raise general public awareness regarding children who suffer from cancer. I hope to accomplish my ultimate goal towards helping shape a positive and adequate perception of this issue, which in turn will benefit the main cause, as well as the lives of patients.

Keywords: children, cancer, foundation, freezing, psychosocial well-being.

Introduction

Cancer is the uncontrolled growth of abnormal cells anywhere in a body. These abnormal cells are termed cancer cells, malignant cells, or tumour cells. These cells can infiltrate normal body tissues. This disease is found in both adults and children. A cancer diagnosis is a highly stressful and painful event for a child and his or her family. It implies intense physical and psychological suffering, generating anxiety, fear, distress, panic, emotional instability, and confusion (Canning, Canning, & Boyce, 1992; Li, Chung, & Chiu, 2010; Von Essen, Enskär, Kreuger, Larsson, & Sjödén, 2000). The oncological disease threatens the natural developmental process, entering the children's life as a disruptive element in their daily lives. It affects their intimate and social dimensions, such as the perception of body image and emotional and social relationships (Di Cagno & Massaglia, 1990; Sources, 1999).

Hospitalization during childhood years can prevent patients from acquiring and internalizing critical skills such as linguistic and narrative capabilities, social and emotional skills, self-perception, and many more (Axia, 2004; Grassi, Biondi, & Costantini, 2003; Perricone, Fuso, Lomonico, Morales, & Polizzi, 2010; Van Cleve et al.,2004). Therefore, they need constant monitoring and long-term rehabilitation.

Strong and healthy relationships with relatives and loved ones, as well as familial support, is crucial for children during this period of their lives. Childhood cancer can affect not only the ill child but the entire family (Williams, Williams, & Williams, 2013). It is therefore vital to consult a psychologist regularly, both for children and their parents, to ensure that psychological help and treatment is carried out properly.

Children with cancer need constant support from the government and relevant organizations. Families are significantly impacted by a cancer diagnosis, however, the financial impact that can be placed upon a family whose child has cancer can lead to a sense of devastation and disruption (Fluchel et al., 2014). They face a lot of problems during treatment, so the government, organizations, and foundations need to ensure that certain problems are resolved as quickly as possible and that treatment is conducted safely and competently.

Methodology

A telephone survey was conducted on April 18, 2021. As the study samples were randomly selected 8 (eight) parents of children with cancer, also, two doctors of German hospital, and one founder of the "Monk Andrew's Foundation". Signed informed consent was obtained from all the study participants. The research was conducted according to the Declaration of Helsinki: For the study purpose, we created different sets of open-ended questions for different participants. The questions for the structured interview were as follows:

The questions for parents:
1) How did you find out about the fund?
2) How / whom did the foundation help?
3) What impact did the Covid pandemic have on the children with cancer?
4) Does your child have a problem with the reproductive system?
5) Do you support or oppose the practice of freezing the baby sperm or egg?
6) Do you think it is necessary for you or your children to see a psychologist?

The questions for the founder of the foundation:
1) Who does the foundation provide support to?
2) How does the fund help the beneficiaries of the month?
3) What impact did the Covid Pandemic have on the Foundation?
4) How important is monitoring for children?
5) How many children have developed a reproductive system problem?
6) Do you think it is necessary to freeze eggs and sperm?
7) Do you think it is necessary to consult a psychologist?
8) Do you provide psychologist's services in the foundation?

The questions for doctors:
1) Do you offer your patients the procedure of sperm and egg freezing?
2) Does the hospital offer psychological assistance to patients and if so, is it effective?
3) What kind of impact did the pandemic have on children?
4) How many patients have a problem with the reproductive system?

Results

According to the founder of the "Monk Andrew's Foundation" and parents, the Foundation helps overweight children, both psychologically and socially. The study population unanimously noted that the Covid Pandemic had a negative impact on both the children and the fund's financial side. The founder of the foundation noted that it is extremely important to store sperm and eggs for children. This is suggested by the clinic doctors. All parents surveyed agree to keep their child's sperm and eggs. It should also be noted that their children do not have reproductive problems because they do not need transfusions of appropriate medications (e.g. dacarbazine). The study population unanimously stated that it is important to consult a psychologist with both children and their parents. As noted by the foundation's founders and doctors, in the last 8 years, a total of 3 teens have had problems with their reproductive system. One of them stored the sperm and today he has a child. Another patient stored the sperm as well, but he passed away. And the third patient did not store sperm and now he is childless. As one of the doctors pointed out, the number of patients that store sperm is small, that the offer is made when the patients are of reproductive age, and also the second reason is that they need to start chemotherapy urgently and just do not have time to settle the relevant documents.

Table 1. Descriptive statistics of parental answers

Q.No	Options	Answers
1)How did you find out about the fund?	From doctor	50%
	From relatives	12,5%
	From TV	37,5%
2) How/ whom did the foundation help?	Psychosocial well-being	100%
3)What impact did the Covid pandemic have on the children with cancer?	Positive	0%
	Negative	100%
4) Does your child have a problem with the reproductive system?	Yes	0%
	No	100%
	Yes	100%

5)Do you support or oppose the practice of freezing the baby sperm or egg?	No	0%
6) Do you think it is necessary for you or your children to see a psychologist?	Yes	100%
	No	0%

Discussion

As research has shown the most important thing is to raise awareness among people about children with cancer and the "Monk Andrew's Foundation". Today, in the social network, we see that many children are taken abroad for treatment when the same procedures can be performed, with high-quality, in Georgia. This is due to the sceptical attitude and distrust of parents towards the Georgian medical field. Thus, it is crucial for the public to get more information about what is being done for these children in Georgia today. As well as to know, that cancer patients are provided with all the necessary resources for modern diagnosis and treatment.

It is also vital for more people to gain knowledge about the "Monk Andrew's Foundation". Nowadays, the "Monk Andrew's Foundation" needs help financially. The foundation's current main project is building a "Happy House"(the only rehabilitation guest house in the entire Caucasus for children with cancer), which requires separate funds. Apart from this, there is no psychologist in the foundation, and raising awareness may help find a professional who will be willing to volunteer for the job.

As we have already mentioned, psychological help is crucial for both children and parents, and the service that today's psychologists provide in clinics is not enough. The children mostly have contact with their doctor, so it's important for the doctor and the child to have a harmonic relationship, which means that the doctor must practically be a psychologist for his patient because he has more contact with than his psychologist does, so it is important to train doctors in this regard.

One of the most significant topics is the freezing of eggs and sperm for cancer patients, especially adults. It is necessary to save eggs and sperm for the patients as soon as possible, because in some cases the patient starts chemotherapy immediately, which does not leave them enough time to settle the legal and financial matters that the procedure requires. Thus this issue needs to be brought to attention immediately.

Conclusion

Children with cancer are assisted by the State, Solidarity Fund, and the "Monk Andrew's Foundation". The study showed that the existence of the "Monk Andrew's Charitable Foundation", alongside the State and Solidarity Foundation, is vital for children with cancer, especially children and their families from regions and conflict zones. It is noteworthy that the foundation provides each child and their family members with housing, food, all the necessary means completely free of cost. The Foundation also understands the necessity of properly monitoring the rehabilitation of patients.

It should be noted that Covid Pandemic has had a negative impact on children with cancer because they are isolated in the clinic, a condition that makes the situation extremely tense. The pandemic also had a negative impact on the fund. The "Monk Andrew's Foundation" relied on donations,

their charitable activities, which took place every September, but could not be held due to the Covid-pandemic. Thus the fund did not receive adequate funds, which created many of the discussed problems.

It is important to save eggs and sperm for cancer patients, especially adults, to respond quickly and they should be able to store sperm/eggs in a short time without any problems. when the cancer patient recovers, then if he or she will have some reproductive problems, he also can have a child. Consulting a psychologist is vital for cancer patients, especially their parents, to be able to deal effectively with this big problem.

The prime goal of my research is to raise general public awareness regarding children who suffer from cancer. I hope to accomplish my ultimate goal towards helping shape a positive and adequate perception of this issue, which in turn will benefit the main cause, as well as the lives of patients.

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Intrinsic aging of the skin. A critical assessment of the role of hormones

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Abstract:
The skin is one of the organs permanently exposed to endogenous and exogenous factors, over time being affected by the aging process. Since the mid-20th century, researchers have sought to discover the influence of hormones on intrinsic aging, their role in preventing and slowing the onset of age-specific signs, and subsequent treatment with hormone replacement therapies, in this way contributing to an increase of the population life expectancy.
From the total number of 90 sources identified in PubMed, NCBI, published from 1994 to 2021, the article is based on 42 of the most relevant ones. The selection was based on the eloquent perspectives of past and present authors and findings on the topic, based on cohort studies, experiments.
The study highlights the influence of hormones on skin homeostasis and their correlation with the mechanism of intrinsic aging, in addition to other endogenous factors such as telomeres, reactive oxygen species, and genetic pathologies. The research aims to evidentiate the role of a variety of hormones whose levels can accelerate or delay the appearance of specific signs of aging: wrinkles, dehydrated skin, and diminished rate of synthesis of collagen and elastin. For example, sex hormones are essential elements in the aging process as the level in the body decreases after the 5th decade of life. Low estrogen levels, mainly in menopause, induce dehydration, loss of elasticity, decrease the ability of the skin to protect against exogenous factors, causing inflammatory processes, accentuation of wrinkles. The low rate of testosterone, especially during andropause, accelerates the signs of aging, causes an increase in adipose tissue and collagenase activity. Oxytocin plays an important role as an antagonist of the inflammatory process, stopping the activity of fibroblasts, cytokines, and allow the fight against reactive oxygen species. Thyroid hormones have relevant activity in the epidermis by influencing the proliferative process and keeping the rate of hyaluronic acid synthesis within limits. The diminution in somatotropin levels in the elderly has a protective role against potentially carcinogenic cells but influences the manifestation of aging. Dehydroepiandrosterone has a function in reducing free radicals. Moreover, it was attested to an anti-inflammatory, anti-cancer effect and increased collagen production. Meanwhile high levels of cortisol show an opposite effect, by inducing the appearance of dark circles, wrinkles, pigment spots.

Science has opted to solve the problems of intrinsic aging caused by the inadequate rate of hormones, by developing hormone replacement therapy. Some of them such as testosterone, estrogen, melatonin, dehydroepiandrosterone have had positive effects, visibly reducing wrinkles, pigment spots, dark circles. However, a considerable part of the replaced hormones induced side effects, from simple irritations to edema, cardiovascular pathologies. Nonetheless, studies continue to identify and resolve controversies associated with hormone therapy.

Keywords: hormone**,** intrinsic aging, replacement therapy, reactive oxygen species, skin.

Introduction

From the past to the present, step by step, everything is constantly changing, from the attitude and mentality of people to the most diverse and incredible technologies designed specifically to withstand the aging process. This topic is addressed by many researchers, and some of the first articles on the factors and processes that induce aging, various disorders, and roles of hormones on senile skin, especially the role of estrogen, date back to 1946, according to publications in the PubMed database.

The skin is a complex, sensory organ that comprises around 1.7-2 m^2 or even more, depending on the person's constitution [1]. It consists of several layers that are equivalent to a barrier that protects the human body from the action of exogenous factors. The outer layer is represented by the epidermis, formed mainly by keratinocytes, among which are melanocytes, being the main factor for protection by creating a biological barrier. The inner layer or dermis, thicker than the previous one, has the role of protection and support of the epidermis. Under that layer is the hypodermis with the function in supporting the skin and of isolation from external temperatures, which means that the skin layer has some significant loads on the human body, primarily protection, thermoregulation by maintaining a constant and favorable body temperature and sensory function of the receiver [2]. Today, beauty is gaining in importance, so September 9 is marked as "International Beauty Day" [3], and over time new formulas and combinations of substances have emerged to keep skin healthy and fight the appearance of deep wrinkles, pigment spots, dehydration, and other skin conditions such as dermatitis, acne in various forms, psoriasis, and eczema.

Although the aging processes of the skin continue, they cannot be stopped, but only "delayed" by using a correct daily care routine and procedures performed at the cosmetology office, as daily use of moisturizer, and those with a protective factor, which prevent the appearance of wrinkles and fine lines due to the protective effect against sunlight, UVB and UVA.

Aging is an inevitable process, due to biochemical changes that occur in the skin over time, inducing a decrease in the levels of collagen, elastin, of important antioxidants such as coenzyme Q, of the hydration level, gradually appearing the first signs of aging. The 21st century is struggling with a global problem called "Pollution". We live in a polluted environment, being constantly exposed to the risk of exogenous factors such as ultraviolet rays, cigarette smoke, stress, unbalanced and irrational eating. The main causes of extrinsic aging, which manifests themselves on our skin in the form of wrinkles, by losing the elasticity of the skin on its entire surface. If we can protect ourselves from extrinsic aging to some extent, then we can control intrinsic aging in much lesser conditions. It is a genetically determined, physiological process characterized by skin dehydration, dermal atrophy, and an increased number of senescent cells [4].

Currently, beauty salons have various mechanisms and solutions to reduce the signs of senile skin, and through appropriate procedures to replenish the epidermis and dermis with nutrients, which would stimulate the production of collagen and elastin, and keep the skin hydrated.

This research targets to analyze and deduce the causes, consequences, and manifestations of intrinsic aging; to present the major role of hormones on the appearance of the skin, and what would be the processes by which they contribute to the appearance of senile skin or vice versa in restoring skin elasticity and firmness and to inform the reader strategies involved in maintaining skin health and shape of hormone therapy for the prevention of intrinsic aging.

Who hasn't heard of Cleopatra or Nefertiti, known as the most beautiful women in the world, or the "fountain of youth" that many explorers and researchers of all time have longed for,

or who wouldn't want to stay forever young and beautiful at the face, or hold the elixir of youth in his own hands?

Over time, scientists have developed new technologies that bring on the shelves of pharmacies and specialty stores various cosmetic products, dermatologically tested to maintain a young complexion, with fewer signs of senility, enriched with active substances that aim to revitalize the skin. Thus, the study is of major importance for familiarizing the reader with the mechanisms of aging and the processes by which we could influence these processes, as well as the special role of hormones in maintaining skin homeostasis, mechanisms at this level, and how they influence senility.

Methodology:

This research is based on recent data and publications in line with those of the 20th century, such as articles from 1994-1995 to 2021. Using the comparative method, it was effective to highlight the opinion of past authors and promising ideas and clarifications of current scientists. The analysis and study of the mechanisms represented by various researchers allowed the exclusion of data less relevant to the study and focused on suggestive and optimal materials to familiarize the reader with new technologies of science in discovering "eternal youth". The articles on which the paper is based are published in databases such as PubMed, The National Center for Biotechnology Information, medical sites, and hospital institutions.

Results:

The skin is an organ that requires special attention, proper care to maintain its shine, uniformity, in order to delay the appearance of wrinkles and maintain its elasticity. On the other hand, with age there is the process of intrinsic aging or also called chronological aging, which is manifested by functional changes in the skin, reflected by decreased production of collagen (type I and III fibers) and elastin [5].

Knowing the basic structure of the skin, consisting of the epidermis, dermis, and subcutaneous layer, researchers have shown that the epidermis is the first to be influenced by the aging processes that occur with age. It becomes thinner, losing its ability to regenerate and produce melanocytes, which causes a reduction in their level and results in pigment spots. Combining intrinsic and extrinsic aging, caused by ultraviolet rays and other exogenous factors, the process of cell degradation and apoptosis is gaining momentum, emerging in the acceleration of the mechanisms responsible for skin aging and cell senescence.

Some of the main causes are inflammatory processes, cellular metabolism, and stress, lack of sleep, dehydration which in turn activates oxidative stress (OS) with the generation of reactive oxygen species (ROS). ROS are responsible for the destruction of DNA, proteins, and cell membranes, which will eventually cause skin pathologies, exacerbate the aging process, and of course, the death of skin cells, thereby reducing the rate of cell and skin regeneration. Free radicals generated by OS processes are usually balanced at the cellular level, by the antioxidant systems present in the body. After all, with age, these systems lose their ability to neutralize free radicals, which in turn dominate the territory causing damage [6].

The same happens if ROS from the mechanisms of mitochondria is no longer eliminated from the body. As a result, are attested mitochondrial DNA changes, mutations, which will negatively influence the energy processes located at the cellular level, leading to dysfunction of other cellular systems. Mitochondria become more susceptible to the action of harmful factors, being injured and consequently cause the first signs of aging [6].

Chromosome changes are removed and stopped due to the presence and activity of telomeres and telomerase in the cell composition. These telomeres have the function of protecting cellular DNA. If these highly necessary components of the cell are damaged by genetic changes, such as deletions, DNA becomes a subject for changes in the negative direction, manifested by senescence and cell death, contributing to the intrinsic aging of the skin. The major causes of intrinsic aging are those that occur at the hormonal level. Hormones with a primary influence that can be mentioned here are growth hormone, estrogen (especially during menopause), testosterone, dehydroepiandrosterone, cortisol, thyroxine, and melatonin [6].

Intrinsic aging is due to damage to basal cells, as the processes of regeneration and proliferation are gradually diminished, in this mechanism being involved fibroblasts, keratinocytes, melanocytes, which as a result will develop cell senescence. Thus, if at the age of 20 collagen production is in the optimal phase, then with the approach of menopause, wrinkles begin to appear in women, fine lines are highlighted, due to the process of "collagen fragmentation", which contributes to skin dehydration, becoming dry and inelastic [4].

Some genetically determined pathologies can promote premature intrinsic aging, among the syndromes responsible for these consequences are Werner syndrome, Cockayne syndrome, Down syndrome, and Hutchinson-Gilford syndrome. Genetic mutations lead to an amplificated rate of skin aging, due to the production of progerin in Hutchinson-Gilford syndrome [4].

One of the major causes of intrinsic aging is genetic, involving not only some changes in DNA but inducing and a disorder of cellular processes. The researchers found that reduced enzyme activity or their mutations are involved in diminishing the antioxidant system to protect DNA from free radical action, more caused by lowering the rate of antioxidant metabolism, reducing the number of antioxidants and their reabsorption from ingested food, but at the same time enhancement in O_2 concentration. Thus, we observe that free radicals can not only come from endogenous sources but as well from exogenous ones, such as ultraviolet rays, smoking, pollution, and lifestyle [7].

Hence, both intrinsic and extrinsic aging works in tandem. Scientists believe that genetically determined aging is only 3% of all causal factors of senility [4]. At the same time, it has been shown that ROS are involved in the process of cell senescence, caused by the decrease in the proliferation rate, as the cells no longer have mitochondrial activity if this function of cell viability disappears. In increasing the concentration of ROS, these phenomena produce nothing more than a "vicious circle" that ultimately leads to cell death. Contrary to these data, it is assumed that in the skin the primary source of ATP is glycolysis, so both the increased amount of ROS, as well as the insufficiency of the antioxidant system are the main causes in the development and promotion of intrinsic aging [7].

Another major factor that induces the intrinsic aging process is the hormonal one. Hormonal activity at different stages of life changes, for example in postmenopausal women, estrogen levels begin to decline. The decrease in the amount of estrogen is the cause of the signs of aging, such as wrinkles and epidermal atrophy. As was mentioned earlier, other hormones involved in the aging process are testosterone, melatonin, cortisol, thyroxine, growth hormone, dehydroepiandrosterone, and oxytocin [8].

Estrogen

One year after the end of the menstrual cycles, menopause sets in, characterized by the production by the ovaries of a much smaller amount of estrogen and progesterone, which implies the aggravation of some skin functions and as a result, the appearance of specific signs of senility [9].

Estrogen levels are particularly important in maintaining the skin's protective barrier, helping to heal wounds and inflammatory processes that occur [10]. The small amount of estrogen affects both females and males. Currently, it is investigated the influences of hormonal replacement of estrogen in accelerated wound healing, but it was proved a negative side of this procedure caused by the development of skin cancer [11]. Healing affected by age is correlated with delayed but excessive inflammation, slowed re-epithelialization, reduced angiogenesis, and decreased fibroblast proliferation and matrix deposition. Since estrogen deficiency will lead to a diminish in collagen synthesis (type I and type III), scientists have tried to find a solution to combat the effects of aging by administering topical estrogen, which would stimulate collagen production and restore the elasticity of the skin [12].

Thus, after analysis, we conclude that estrogen is a major factor in maintaining skin homeostasis, hydration, and elasticity, even at an advanced age, topical application of which aiming to prevent and treat the signs of aging [13].

Oxytocin

Another hormone, which is less studied, is oxytocin, considered to possess the ability to protect the skin from factors that would predispose to aging, by suppressing the secretory phenotype associated with senescence (SASP), preventing the senescence of normal human dermal fibroblasts (NHDF) and in general, intrinsic aging [14].

Oxytocin or the so-called "confidence hormone or love hormone" is not only involved in the process of birth by stimulating the muscles of the uterus, or in maternal behavior but also aging, now becoming the target of new studies on its use to stop senescence of fibroblasts in correlation with inhibition of pro-inflammatory cytokine activity [15] and muscle repair [16].

The active involvement in combating the inflammatory processes of the hormone neuropeptide oxytocin (OXT) requires scientists to analyze the situation in which OXT could be used against processes that cause senility, this field is not yet experienced on human skin. The OXT receptor located in both dermal fibroblasts and keratinocytes once released, leads to decreased glutathione levels in the skin, resulting in excessive growth of ROS, which is directly involved in the processes of accelerating senescence. Thus, some research shows that the reduced activity of OXT is correlated with inflammatory manifestations of atopic dermatitis and sensitivity to OS [17]. We note that oxytocin is not only the intermediate due to which the maternal and parental connection is made, but in the future, it could still be used in treatments against the signs of aging.

Testosterone

If in women one of the main causes of intrinsic aging is the decrease in estrogen levels, especially with the onset of menopause, then the decrease in testosterone levels is among the triggers of the aging process in men. Andropause is characterized by a remarkable decrease in testosterone, starting with the 5th and 7th decade of life, manifested primarily by decreased libido, osteoporosis, sometimes obesity, but moreover by deepening signs of aging, such as wrinkles, quantitatively minimal collagen, and elastin, dehydration. At the same time, in the body of a male, the amount of estrogen is increasing. Testosterone has the property of joining to certain types of globulins that are responsible for binding to the sex hormone, triggering the andropause and signs of aging [18].

Despite the desire to be eternally young, studies have concluded that the topical use of cosmetic products based on active substances such as testosterone does not have a positive effect on the skin, as it often causes dermatitis and various irritant reactions. Though, science does not

give up and focuses on researching a potential product that could be used successfully in cosmetics without side effects and mainly for anti-aging. The element that captured the researchers is "honokiol" which through various cellular mechanisms of self-inhibition would increase testosterone production, and in combination with its antioxidant, anti-inflammatory, and muscle relaxant properties, could be used as an active substance in cosmetics, especially for those in the eye area with a concentration of 1%. Thus, following the experiments, the effect of honokiol on wrinkled skin was observed by restoring the dermal layer, and visibly reducing wrinkles, especially those around the eyes [18].

"Since the time of the ancient Egyptians and Romans, it is believed that the products of the testicle act as aphrodisiacs and as a fountain of youth to increase physical strength and reverse the effects of aging" [19]. If in the past, testosterone began to be used in pill form, it is now administered in various non-oral forms, such as gels that are applied to the upper limb, creams, patches, or injections. This is explained by the fact that if administered orally, it is slightly soluble in water and cannot be absorbed, causing hepatotoxicity, and because the liver is the one that metabolizes it [20].

Thyroid hormones

Thyroid hormones are as well part of the process of proliferation, development, and maintenance of epidermal function in the process of treating lesions. In this manner, the thyroid-releasing hormone and thyroid-stimulating hormone are directly involved in the gene expression of the skin [21].

With age, there are some disorders in the thyroid gland and the production of the hormones thyroxine (T4) and triiodothyronine (T3), which participate to some extent in the processes of homeostasis of the skin. In some pathologies related to abnormal levels of thyroid hormones, the skin becomes thin, in some cases rough, however, situations of accumulation of hyaluronic acid and causing edema in the skin have been detected. Research on the topical administration of components that have the hormone as an active substance has shown that it increases the rate of wounds healing, based on T3 and T4. The changes that occur with these pathologies, expose the skin to an early aging process due to damage to the skin layer, continuously subjected to metabolic effects [22].

Growth hormone

Recent studies have made a close connection between the process of intrinsic aging and that of neuroendocrine aging, which has been shown to correlate with the defense against carcinogenic action that could develop in cells of the human body and those associated with symptoms of senility, depending on low levels of growth hormone (GH). Some research based on the experimentation of laboratory mice states that the absence of GH can prolong life and slow down aging, while elevated somatotropin levels are associated with the likelihood of developing various diseases and an increased rate of early signs of aging [23] [24].

Over time, there are several changes in the human body, including a decrease in muscle mass, but for this problem, scientists have found the solution by injecting an amount of GH solution that would help increase muscle mass and regenerate the lipid layer at the skin level, in that way being used in anti-aging treatments, but again with some side effects. However, according to the data associated with the administration of GH, "prescribing GH to endocrinologically-normal middle-aged or elderly individuals to delay or reverse aging is generally considered futile, unethical, and, in the United States, also illegal " [23] [24].

Despite several contradictory hypotheses, a variety of experiments have been performed

that have determined that increased GH levels would negatively influence, in particular, the fact that it would enhance the rate of the senility symptoms onset, while stopping the administration of GH, on the contrary, would increase longevity by reducing the level of cellular senescence and subsequently inflammation, a decrease in the rate of insulin secretion which will increase its sensitivity, by increasing the level of adiponectin and antioxidant enzymes correlated with increased resistance to stress [24].

Thus, due to the side effects caused by somatotropin supplements, researchers are studying the possible actions of this hormone in the form of a recombinant growth hormone (rhGH) as an alternative to anti-aging treatments. Decreased GH levels are normal at an advanced age, they have, in particular, a protective role of the body, its insufficiency is manifested by changes in the composition of the skin. As we can see, the additional administration of GH induces both positive effects and many harmful effects on health, and some mysteries that the hormone hides in anti-aging treatments will still be elucidated [25].

At present, the use of GH substitution is used only for people of small stature, but despite the laws imposed by the International Olympic Committee and other anti-doping agencies, they are administered and by some athletes as injections to increase physical performance [26].

The fight against the signs of aging with the help of the miraculous GH is not one of the safest, neither injected nor in the form of capsules, such as the famous SeroVital which for some reason gained popularity on the market due to the effect on the skin by reducing fine lines. and wrinkles, providing energy to the body and revitalization, being a support for the immune system, but which has side effects from simple fatigue and muscle pain to edema, numbness, carpal tunnel syndrome. Moreover, increasing GH levels used for a long time could predispose the body to various diseases and cancers [27] [28].

Dehydroepiandrosterone

In a direct correlation with the appearance of signs of senility comes the level of dehydroepiandrosterone (DHEA) in the human body, which induced the idea of scientists to involve the use of DHEA in topical anti-aging treatments. DHEA is a hormone produced by the adrenal cortex, essential in the process of homeostasis. There is withal an important link between collagen production and DHEA levels because if DHEA decreases, it attested a lower rate of pro-collagen and extracellular matrix synthesis and as a result, the first fine lines, wrinkles, and pigment spots, including skin dehydration and decreased elasticity [29].

To reduce and delay these processes, specialists have developed several products that have DHEA as an active substance in various concentrations to increase collagen production and improve the lipid layer, which will protect the skin from dehydration by preventing evaporation. In addition to the anti-aging effect, it still has antioxidant properties, helping to minimize the number of free radicals, but in treating wounds and protecting DNA. Other benefits include the fact that DHEA associated with G protein contributes to the inhibition of the apoptotic process in the epidermis. A concentration of 5% is used not only in anti-aging products but also applied in the prevention of breast cancer or other types of cancer, possessing anticancer and anti-inflammatory effects. Thus, to increase its effectiveness, a 2005 study shows that DHEA combined with cyclodextrins enhances its solubility and permeability to topical administration of the product, involving an active process of keratinocyte proliferation. With these successes, researchers continue to discover new ways to administer it to amplificate its effectiveness [29].

The so-called “youth hormone” has been used in various experiments in concentrations of 0.1%, 0.2%, 1%, and 2% as a cream applied to the skin, proving that it is involved in increasing the expression level of pro-collagen. [30].

Some studies indicate that consuming 50 mg a day of DHEA-based supplements not only delays the signs of aging, but of neurodegenerative diseases, increases the effectiveness of memory, antiviral function, libido, reduces abdominal obesity, but primarily improves skin appearance, offering it shine and minimizing wrinkles, by increasing collagen production and sebum secretion which has an antimicrobial effect [31].

Cortisol

Stress is one of the biggest enemies of the current generation, a health hazard and accelerator of the aging process. Some have become accustomed to the stressful way of life, for others, this sphere requires multiple measures to not affect their emotional state.

The skin is the organ affected from 2 points of view by the stressor, the one caused by ultraviolet rays (exogenous) and the emotional one (endogenous). Medical researchers have also demonstrated the key elements of the correlation between stress and its effects on the skin, namely cortisol or the so-called "stress hormone". Exposure to these factors involves an increase in cortisol levels, especially in the skin, by activating 11-beta-hydroxysteroid dehydrogenase type 1 which will result in increased cortisone and decreased collagen synthesis in the skin layer and the number of fatty acids and ceramides. Activation of Nf-kBs will favor the production of ROS, which once present will lead to the appearance of wrinkles, pigment spots, dark circles, and bags under the eyes [32].

However, the skin has enzymes specifically designed to fight ROS, such as hemoxygenase-1 which will prevent apoptosis and provide the antioxidant capacity needed to lower the levels of ROS produced by both exogenous factors, as well as endogenous. Against the signs of aging caused by increased levels of cortisol, scientists have discovered a plant with special properties in the fight against these signs, by reducing wrinkles and dark circles, and increasing the level of dopamine and endorphins (beta-endorphins), while involving reducing the level of cortisol. This miraculous plant has its etiology in India under the name of *Tephrosia purpurea*, and with immense popularity among anti-aging cosmetics and amazing effects on the skin, improving its homeostasis [32].

It is known that the release of cortisol negatively affects the skin by causing inflammation, acne, and excessive sebum secretion by the corticotropin that blocks the pores. The stress can withal be the cause of rosacea and psoriasis. Thus, at the skin level, we can adopt measures for skin regeneration and revitalization through cosmetological procedures such as micro-needling and enzymatic and chemical peels, various facial treatments that include laser, and at the level of the whole body by practicing physical exercises, meditation, outdoor walks and other activities that would facilitate the regression of stress [33].

Melatonin

In addition to the listed hormones, keratinocytes, melanocytes and fibroblasts also have considerable amounts of melatonin receptors, but after the 4-5th decade of life, melatonin levels begin to decline. Melatonin has an important value in maintaining and regulating the heart rate, considered to be a key element in the fight against ROS and cancerous tumor cells [34]. Melatonin biosynthesis occurs in the skin under the action of tryptophan hydroxylase (1 and 2) which converts tryptophan to 5-hydroxytryptophan, after which in the presence of the cofactor pyridoxal phosphate and DOPA decarboxylase, 5-hydroxytryptophan is reduced to serum. As a result of the acetylation process serotonin is converted to N-acetyl-serotonin, and subsequently to melatonin under the influence of hydroxy-indole-O-methyltransferase. With its presence in the epidermis and when both UVA and UVB sunlight cause ROS to multiply, melatonin plays a major role in fighting

free radicals by its ability to interact with them to form N1-acetyl-5-methoxykynuramine (AMK) or N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK), which possesses antioxidant properties and reduces protein oxidation, lipid peroxidation, and oxidative DNA destruction. Thus, it has been shown that melatonin administered before contact with UV rays is directly involved in preventing their damage to the skin. In this way, topical application of melatonin-based products is used to slow down the appearance of signs of aging and protect against UVA and UVB rays, due to their antioxidant, anti-inflammatory, and anti-carcinogenic properties [34].

As well as the role of melatonin in regulating sleep, preventing alopecia, protecting against cardiovascular disease, Alzheimer's and osteoporosis, it plays an exceptional role in the homeostasis of the pill, giving it anti-aging benefits and protecting it from photodeterioration [35].

The use of oral supplements, but especially topical products have proven effective in combating wrinkles and dry skin, protecting against dehydration, and maintaining the necessary concentrations of collagen, elastin, even when used on the entire skin surface of the body is safe. But do not forget that sleep is a significant element in the process of skin regeneration and repair, and sleepless hours will decrease the rate of melatonin synthesis accelerating the aging process, so at night, melatonin activity becomes more intense and non-compliance with the circadian regime will influence the rate of sleep. expression of melatonin, by manifesting the consequences on the skin, nervous system, and human body in general [36].

Discussions

Intrinsic aging is correlated with a wide variety of causative factors, but it often works in tandem with exogenous ones that promote extrinsic aging. Aging, like other phenomena in the human body, is genetically determined, but under the influence of these factors, there is an acceleration of the process. To reduce this dilemma among humans and give them a portion of the "elixir of youth", scientists resorted to several methods to slow down and treat the signs caused by aging.

First of all, a correct care routine is needed, which includes products specific to the skin type and age, such as micellar water, washing gel, toner, antioxidants, alpha- and beta-hydroxy-based peels, acids (AHA & BHA), serums based on nutrients, hyaluronic acid, argan oil and rosehip seeds, Argireline, retinoids, peptide complexes, and last but not least sunscreen cream and dietary supplements. The sunscreen cream will help protect the skin from photoaging; retinol and retinoids are used to reduce fine lines, improve skin texture and tone by stimulating collagen production and neutralizing ROS; antioxidants such as ascorbic acid, niacinamide, coenzyme Q10, vitamin E, resveratrol, glutathione, and ferulic acid will fight free radicals and will also contribute to some extent to protection from the sun's rays; the caffeine solution is used against dark circles. Lasers, CARBOXY procedures, correction of deep wrinkles by injecting hyaluronic acid or botulinum toxin (by inhibiting the release of acetylcholine at the synaptic level and resulting in muscle relaxation) are widely used for a period of 3 to 6 months but the effect depends on each individual.

However, science has not only limited itself to these but has introduced hormone replacement therapy (HRT). Over time, a particular concentration of hormones begins to regress, DHEA, GH, thyroid hormones, estrogen, testosterone, melatonin having the main implications as determinants of intrinsic aging. For example, DHEA therapy has produced multiple benefits on skin texture and appearance, but has also led to increased libido; GH in the experimental phases showed a slowdown in the aging process, withal, in the case of this hormone there are several question marks and uncertainties about the effects it produces, especially the negative ones. HRT

with melatonin has been very successful not only in treating insomnia but in senile skin, by reducing fine lines, wrinkles, increasing collagen synthesis, and moisturizing the epidermis and dermis. Testosterone, among others, is one of the most recommended substitutions with the installation of andropause to reduce fatigue, increase libido and even improve the appearance of the skin [37]. HRT with testosterone has gained great popularity, especially the method of using "testosterone pellets" or "testopel", in which a pellet contains 200 mg of crystallized testosterone, and a dose for a man is around 1200 mg introduced into adipose tissue, which will have activity for 5-6 months, and for women around 3-4 months. Creams and gels are used once or twice a day on more sensitive areas of the skin, while injections once a week [38].

HRT with estrogen can be adopted in various forms, from suppositories, pills, patches to gels, creams, and injections, especially being used by menopausal women, but likewise by transgender people to feel comfortable. The pills are the most common, including those based on estradiol or estrogen conjugate (Premarin - it is also created in the form of creams) that are used once a day; the patch is replaced once or twice a week depending on the patient's condition, compared to pills, the patch does not cause susceptibility to liver disease or the formation of blood clots [39].

A study based on Premarin cream and its effects on the skin showed that the level of skin thickness increased and fine lines reduced, improving the appearance of the skin, by restoring elasticity and treating pigment spots [40]. However, creams and gels, like the rest of the methods, predispose to the possible development of cancer. In connection with these suppositories, they are used twice a week, and the vaginal rings are changed every 3 months [39]. Some studies based on HRT with estrogen have concluded that after oral administration, not only the thickness of the skin increased but also the production of collagen. Even its topical use has recorded such results and the development of elastic fibers in the skin. Nonetheless, research continues and is looking for solutions to the side effects of this therapy [41].

The therapy of the other hormones involved in the phenomenon of intrinsic aging remains to be studied due to the undesirable side effects it has on the body and the uncertainty of the mechanism of action of these therapies on the activity of hormones organs. Androgen replacement therapy, GH, IGF-I, progesterone, melatonin, cortisol, and thyroid hormones remain controversial. [42].

Conclusion

Life expectancy, for most countries in the world, is continuously increasing, thanks to new technologies that have helped maintain the body's health, and which has facilitated delayed aging from a smart perspective, through a healthy lifestyle and a proper care routine. Who wouldn't want to stop time instead or, even better, go back a few years to see themselves young again and without signs of senility?

Science has won people's hearts and fulfilled their desire to have access to the "fountain of youth" through the possibility of using various procedures for rejuvenation, revitalization, and regeneration of the skin, through access to products that would facilitate the reduction of wrinkles, fine lines, dark circles, and pigmented or post-acne spots, which would result in skin toning and increased skin vascularity. HRT has become an incredible opportunity to alleviate the signs of aging, because, with age, the rate of a whole series of hormones start to diminish, predisposing the person to the development of various pathologies and decreased skin tone, elastin, and collagen production, of the protective barrier that becomes more sensitive to the action of external factors, such as UV rays and pollution, accelerating the aging process and exposing the DNA to damage.

Controversy continues to arise, but researchers are constantly looking for solutions to the

harmful effects that HRT can cause on the whole body. With technical and scientific progress, the contemporary world has broadened its horizons of knowledge, and scientists have begun new research in the field of skin diseases, intrinsic and extrinsic aging, understanding and elucidating the mechanisms related to dermato-endocrinology, and the influence of the hypothalamus and skin homeostasis of hormones.

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Artificial Blood: The Future of Blood Transfusions?

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Abstract

Blood is the major constitutes of body fluid and most importantly it is the connective tissue which also supply oxygen to our cells and carries carbon dioxide from cells, not only this blood also plays vital role in coagulation cascade wound healing and fighting against pathogens. Now depletion in this body fluid can cause several problems which can be life threatening to avoid such life-threatening condition blood transfusion is used but as we grow deficiencies of transfusable blood is alarming in many countries' towns and cities. To deal with it artificial blood comes into action which gives advantages like easy storage long life easy transport and also acts as a counter to some religious believes, but with every innovation it has own advantages and disadvantages out of which disadvantages like cost viability, proper resources and physiological conditions like raises in blood pressure, gastrointestinal dysmotility, Jaundice. Though artificial blood is in experimental phases yet but surely it would drastically change the healthcare in upcoming future if it taken into practice.

Keywords: Artificial blood, blood donation, Jehovah's witness, Perfluorocarbon, Hemoglobin based product.

Introduction

Blood is the transportation system of our body every metabolic process starts with blood and ends in blood. Blood provides the essential raw material to every cell for metabolic process and carries the waste product after the process is complete. The fundamental and most significant undertakings of blood is to supply oxygen all through the body to each organ and every cell and afterward to deliver the oxygen to tissues, gathering the carbon dioxide in its stead. The entirety of this is accomplished through haemoglobin, the oxygen-conveying protein contained inside red platelets (erythrocytes). The other cell parts of blood are white cells, which are significant for the resistant

reaction, and cell pieces considered platelets that are vital for blood thickening and wound recuperating.

There are circumstances when body runs outs of blood or there is a blood shortfall in our body like injury, suggestive pallor, intense sickle cell emergency, and intense blood loss of in excess of 30% of blood volume, which can additionally cause manifestations like decreased breath, confusion, congestive cardiovascular breakdown, and diminished exercise resistance. To tackle these situations medical healthcare came up with a solution which was lifesaving and beneficial for human race that intervention was “Blood Transfusion”. In any case, each research accompanies its own benefits and limits out of which blood transfusions have restrictions, for example, it should be put away at a cool temperature and it has a time span of usability of just 42 days. In view of issues referenced before blood may not be promptly accessible in cases like a crisis — on the combat zone or in an emergency vehicle transferring a harmed, bleeding patient to the clinic.

"Necessity is the mother of invention”. As we know that blood donations have its own barriers and there has been a major need for a substitute to reduce a dependency on a human body for blood. This is where introduction of artificial blood will play its major role. At this point of time artificial blood comes into play. A blood replacement (also known as artificial blood or blood surrogate) is a material that mimics human blood and performs certain of its functions. It plans to be a swap for blood transfusion, which includes the exchange of blood or blood-based items starting with one individual then onto the next. There are no very much acknowledged oxygen-conveying blood substitutes right now, which is the standard goal of a red blood cell transfusion; however, non-blood volume expanders are commonly available for situations where only volume regeneration is needed. These are assisting physicians and surgeons in avoiding infectious transmission and immune suppression, as well as addressing the chronic lack of blood donors and discuss the religious opposition to consuming transfused blood held by Jehovah's Witnesses and others.

Hypothesis

1. Artificial blood can be a complete substitute of blood donation.

2. Artificial blood would reduce the dependency on humans

Literature review

Use of a blood substitute other than human blood for transfusion is not a new concept. Around the end of 16th century, Sir Christopher Wren gave the idea of using various substances that could replace human blood. Squires, J. E. (2002).

The 21st century is not very easy for today's generation. Expansion in inhabitants, population aging, group of new infectious agents and shattering events are some dejection factors for the present status of blood transfusion. Apparently, it seems that science and research not only could bash these problems but in count would turn plentiful human dreams to reality in such manner. Researchers take that one of things that can be established in future could be false blood substitutes that may change the whole concept of blood transfusion. Moradi, S., Jahanian-Najafabadi, A., and Roudkenar, M. H. (2016).

Artificial blood was introduced next to the upsurge of HIV in 1980 because of the threat of its spread by blood transfusion, which forces greater expenses because of the tests. Sharma, A., Arora, S., Grewal, P., Dhillon, V., Kumar, V. (2011).

The ideal artificial blood has the accompanying qualities. In the first place, it should be protected to apply and feasible inside the human body. This indicates that distinctive blood orderings would not make any alteration when an artificial blood is utilized. It likewise suggests that artificial blood can be handled to eliminate all diseases, for example, infections and microorganisms. Secondly, it should have the option to transport oxygen throughout the body and deliver it to the destined organ. In contrast to donated blood, artificial blood can be kept for a longer time, a year or more this is a major difference among normal blood and artificial blood. There are two essentially various products that are at work in progress as blood replacements. They vary basically in a manner that they transport oxygen. One is contingent to PFC, whereas the other is a haemoglobin-based item. Sarkar S. (2008).

Perfluorocarbons (PFCs) are artificial products produced from fluorine and carbon comprising synthetic compounds. They are synthetically idle, however more convincing than water or blood plasma in dissolving and retaining oxygen in the lungs and afterward moving oxygen throughout the body. PFCs stay in the blood for around 2 days.

Oxyglobin is a solitary blood reserve endorsed for usage in veterinarian medication in the US and Europe. A protected and powerful blood surrogate is direly required for human blood transfusions

in clinics, at calamity destinations, and on battle zone filled with harmed military soldiers. A proficient oxygen-mobilizing blood substitute for people would likewise be a significant treatment for aplastic iron deficiency and swollen tissues in sickle-cell weakness.

Artificial blood has quicker and improved oxygen conveyance. These atoms permit complete oxygen transport following bonding as contrary to stored blood which entails 24 hours to achieve max oxygen conveying limit because of the consumption of 2,3 – diphosphoglycerate.

Low affinity for oxygen allows fast deposition of oxygen in the tissues. They can guarantee satisfactory oxygen conveyance at haemoglobin levels of 2 gm/dl without unfriendly impacts.

It has Lengthier Shelf Life: These could be put away on room temperatures for extended periods of about 1 to 3 years and are fit to be utilized when related with stored blood which can be put away for around 35-42 days. Here, there is no necessity of refrigeration of the items.

It has general congruence: Because all the protein segments are eliminated, our immune system doesn't remember it as a foreign or unfamiliar substance. Subsequently the need of similarity testing dependent on blood groups is stayed away from. The chance of errors which may bring about incompatible blood transfusion is additionally sidestepped.

Stoppage of Transmission of Infectious/Anaphylactic specialists: Products are cleaned, then consequently odds of viral or illness transmission are lightened. Reduction in ischemic, inflammatory and reperfusion injury. Haldar, R., Gupta, D., Chitranshi, S., Singh, M. K., & Sachan, S. (2019).

Adverse reactions and restrictions in the utilization of oxygen-conveying arrangements

Adverse reactions related with hemoglobin-based items contain raises in blood pressure, low movement in gastrointestinal tract, and gentle, brief expansions in pancreatic catalysts. Patients additionally experience jaundice because of grafting of free hemoglobin. Treatment with PFC-based items can result in gentle thrombocytopenia i.e., 10% to 15% decline and a flu-like condition. Because patients ought to be on high levels of oxygen while PFCs are utilized, the danger of oxygen injury exists with delayed administration. Since human phagocyte can take up these two things, there is also the notional risk that phagocyte ability will be changed.

All types of artificial blood have a short life span i.e., enduring just around 24 hours in the flow and are over the top posh, i.e. estimates at $500 per unit. Lastly, utilization of mentioned items can meddle with systematic laboratory testing. Hemoglobin arrangements will cause the patient's blood samples to seem haemolyzed, and PFC preparations would lead to lipemia.

A minor group of individuals having a place with a specific religion, called Jehovah's witness don't allow blood bonding or blood items, considering scriptural readings. At the point when such congregation of individuals is needing medical care, their certitude and belief is a snag for their appropriate therapy, and stances legal, ethical, and medical challenges for going to medical services In light of the fast improvement in the enrolment of this social occasion all throughout the planet, specialists going to crisis centres should be set up to supervise such patients. At present, there are more than 7.5 million JW universally and about 37,913 in India, and their number is quickly expanding. At the point when gone facing with such game plan of patients, blood free huge operation will be an unfathomable test to both the sedative and careful groups. It is fundamental to explain all the available options in contrast to patients who reject blood and blood items. Chand, N. K., Subramanya, H. B., & Rao, G. V. (2014).

Different manufacturers have items in clinical trials; be that as it may, not really safe and effective counterfeit blood item is at present advertised. It is predictable that if a counterfeit blood item becomes accessible, it will be around yearly sales of more than $7.6 billion in the United States alone. Sarkar, S. (2008).

Methodology

A total of 126 Individuals of aged 18 to 60 participated in this study, from which 56.3% were female & 43.7% were male participants. We used both quantitative as well as qualitative method, by Google Forms for our survey in April of 2021. We aimed to study the tendency of local people for blood transfusion, and we also gathered views of practicing doctors regarding artificial blood.

We, in our survey, used close ended questions, open ended questions and multiple-choice questions in order that people get more involved and answer to the survey correctly & honestly. Sampling frame was not specific, anyone was open to take part in the survey, conducted in Google Forms pattern. For the survey, we achieved the role of participants, by sending the questionnaire on social media. For example, WhatsApp, Instagram, and Facebook.

Data analysis

Among the total participants which is 126, 55 were male and 71 were female. The respondents were mainly from countries India and Georgia. The main age group for the survey was from 18 to 60 years & out of which 84.9% were of age group 18-30 years, 8.7% were of age group 31-40 years, 4.8% were 41-50 years and the rest 1.6% were 51-60 years. About 65% of our participants were university students and 28.6% were graduates. 5.6% of participants were literate, and 0.8% were unschooled. Out of 126 participants, 87 were Hindu, 5 were Muslim, 31 were Christian, and 3 others. From the responses 55 participants have donated blood. On asking how frequently you donate blood 8 of the participants donate blood every 6 months, 8 donate blood twice a year, 31 participants donate blood once in a year, 5 donate once in two years. Among the responders 71 have never donated blood. We asked our participants, if someone close to you needs blood would you donate, for which, 114 said yes, 6 said no and 6 were not sure. On contrary, we also put forward a question if someone who is NOT close to you needs blood would you donate, 87 responded yes, 10 said no and 29 responded maybe. Among our participants 28 have received blood transfusion. We asked participants, do their religious beliefs interfering in receiving or donating blood and 9 of them responded yes. In one of our questions we tried to figure out whether generalized population is willing to receive treatment with artificial blood out of which 51.6% were willing to receive the blood substitute, 6.3% refused and 42.1% were not sure.

Discussion

As we mentioned earlier deficiency of blood for transfusion and reduce tendency of people to donate blood would eventually lead to blood shortage and can massively affect healthcare in situations like pandemic. In our survey we also observed that over 56.3% of the participants haven't donated blood yet. In situations like pandemic, blood drives across the country were cancelled, leading to hospitals running low on blood. Even there are ethical issues with specific communities where their religious beliefs don’t allow blood transfusions. Among this, a very well-known dilemma is with Jehovah’s witness. They believe that it is against God’s will to donate or receive blood. In our survey around 7.1% of participants have a similar tendency or approach towards blood transfusions. To respect patient’s autonomy and human rights doctors are forced not to give blood even in life threatening situations. Now here comes the advantage, if artificial blood comes in action, there’s a certain probability that this blood would not be considered as a substance from

others body, it would be considered as a laboratory product and healthcare can be achieved without hindering their religious beliefs.

In our survey we also encountered obvious results that over 90.5% of the participants would donate blood if someone close to them needs blood but over 69% of the participants were willing to donate blood to those who are not close to them. This shows that people tend to donate blood in emergency situations to save their close ones, which means that there's a decrease of 21% of the participants when it's not their concern. We tried to figure out the mentality of the general population by asking them will they prefer artificial blood; we received an astounding response of over 93% of participants were convinced and over 51% gave a strong positive response. If in future artificial blood passes the human trials and is recruited in the healthcare, then a positive feedback from the patients would be observed which is indicated in our survey.

Conclusion

Now we have seen what artificial blood is and how it is made, what are the advantages and limitations. We saw that artificial blood has not been able to reach the goal of replacing donated blood as it doesn't have all the cells which are present in donated blood and human blood do many things like closing wounds ,fighting infection and main function of transporting Oxygen. But the Artificial blood can only transfer Oxygen throughout our body. So, we can see that artificial blood cannot completely replace donated blood. However, in future it can be a huge help in situations where patients have lost significant amount of blood and doctors will not have to depend on blood banks or patients' relatives for blood. It can also pose as a strong argument in cases where religious belief is an obstacle in treating patients with end stage diseases. To summarize, we can strongly conclude that artificial blood cannot be complete substitute of blood donation yet, but surely our survey concludes that it would definitely reduce dependency on humans.

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Annexure I

- Age *

18-30
31-40
41-50
51-60

- Gender *

Male
Female

- Nationality *

Indian
Georgian
Other:

- Religion *

Hindu
Muslim
Christian
Other:

- Qualification *

Literate
University student
Graduate
Unschooled

- Do you donate blood? *

Yes
No

- If yes, how frequently do you donate blood? *

Every 6 months
Twice in a year
Once in a year
Once in 2 years
Haven't donated

- If someone close to you needs blood will you donate? *

Yes
No
Maybe

- If someone not close to you needs blood will you donate? *

Yes
No
Maybe

- Have you ever received blood transfusion? *

Yes
No

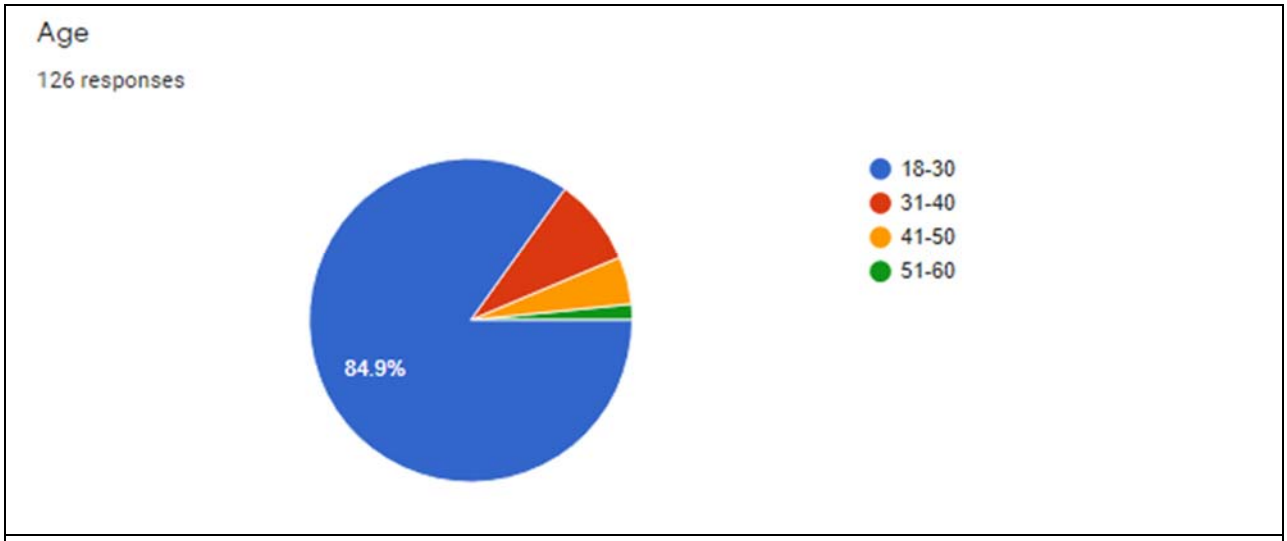
- Do your religious beliefs interfere in receiving or donating blood? *

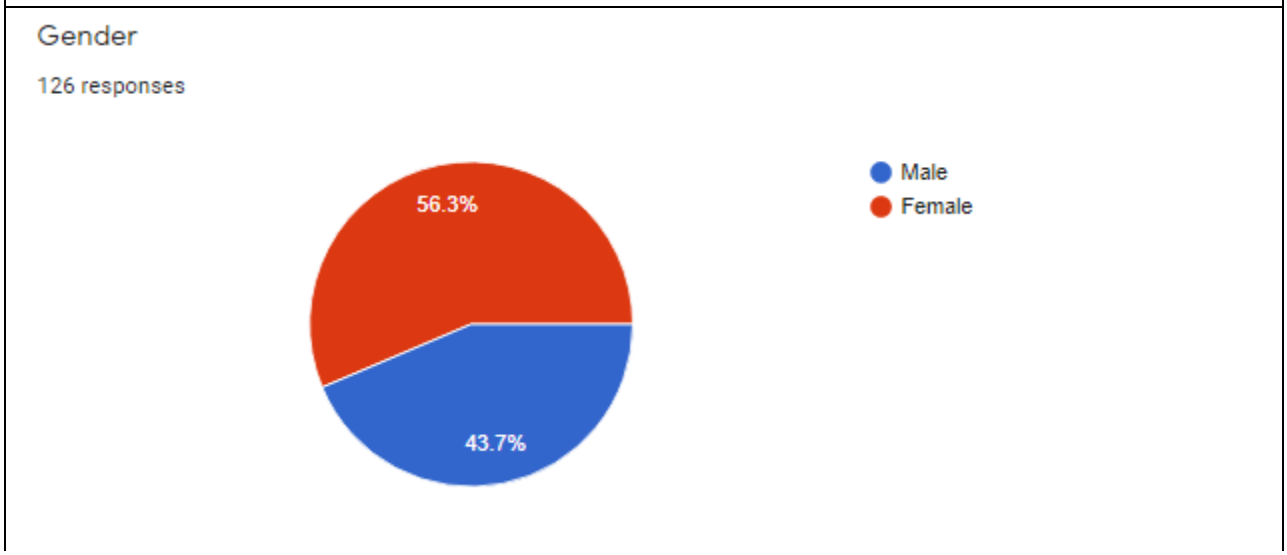
Yes
No

- In future, when synthetic blood (substitute for normal blood) will be available, will you accept it? *

Yes
No
Maybe

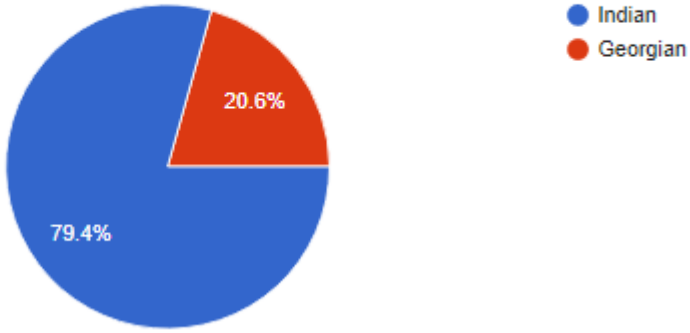
Annexure II





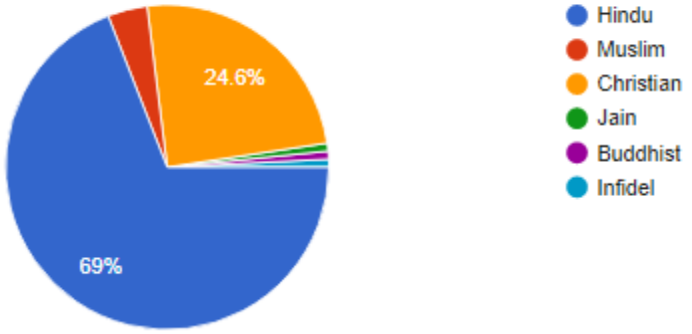
Nationality

126 responses



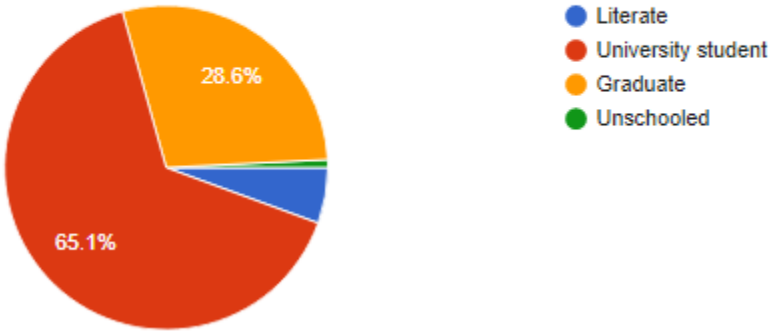
Religion

126 responses



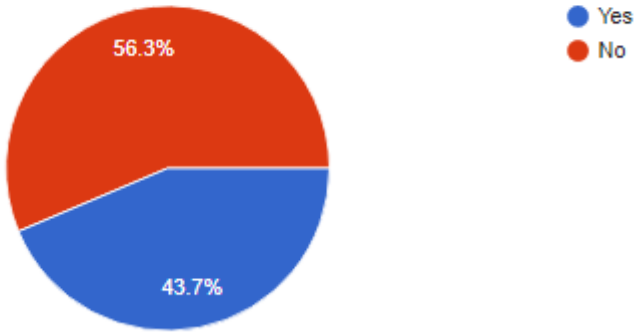
Qualification

126 responses



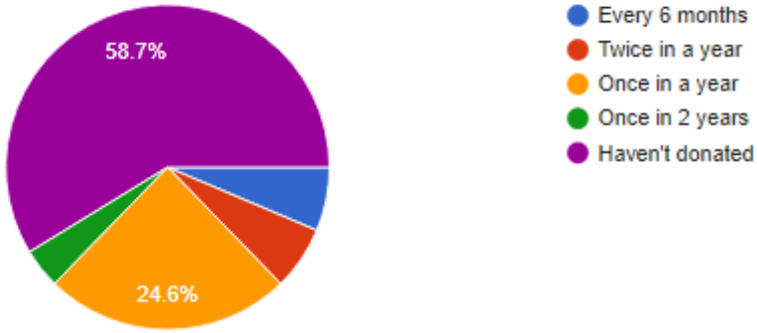
Do you donate blood?

126 responses



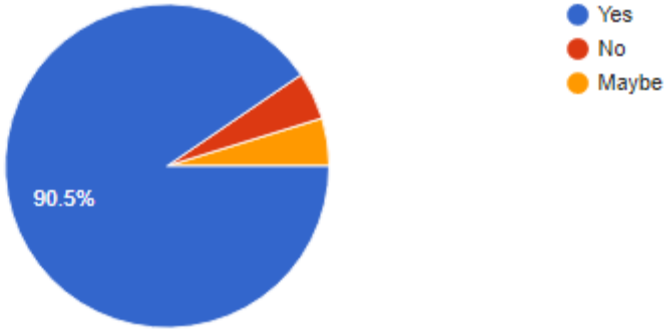
If yes, how frequently do you donate blood?

126 responses



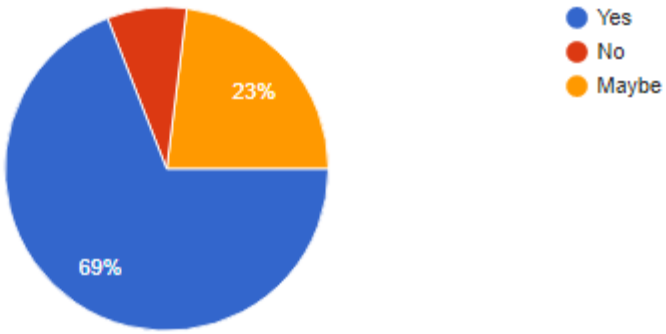
If someone close to you needs blood will you donate?

126 responses



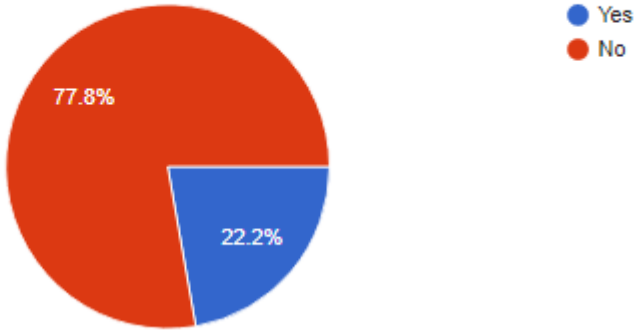
If someone not close to you needs blood will you donate?

126 responses



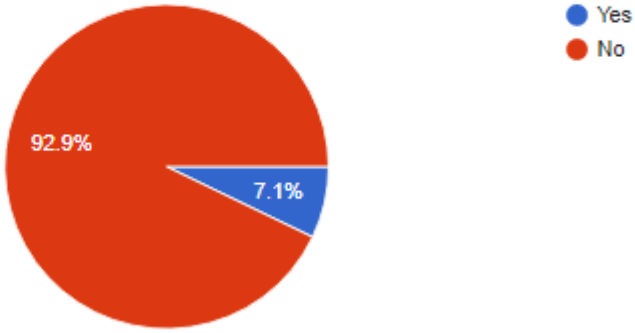
Have you ever received blood transfusion?

126 responses



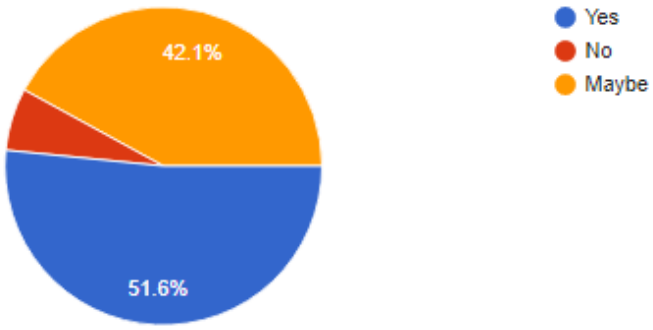
Do your religious beliefs interfere in receiving or donating blood?

126 responses



In future, when synthetic blood (substitute for normal blood) will be available, will you accept it?

126 responses



The Psychosocial Impact of Wounds and the Nile Tilapia

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Abstract:

Current healthcare systems fail to offer scar-reduction as part of their burn injury healing process. The psychosocial impact of burn injuries on victims have been widely discarded, and their psychological effects have not been wholly recognized. There are recent, more alternative techniques being introduced to reduce scar formation in burn victims. The technique being discussed in this paper is of the Nile Tilapia fish skin (NTFS) xenograft that offers high collagen and reduced scar formation. In this context, we review researches conducted on the mental repercussion of burns on self-esteem and quality of life in victims, as well as the role of collagen and NTFS in burn injury recovery and scarring. Then, we proceed to conduct a small research on the relationship between burns and self-esteem, assess willingness of using NTFS as a treatment modality, and question the need for healthcare systems to include reduced scar-formation maneuvers as part of their treatment protocol for burns.

Key words: NFTS xenografts, burn, injury, self-esteem

Introduction:

Background

In modern day society, the notion of beauty is modifying into an art of impeccability. From women seeking alternatives to reverse aging to men pursuing different methods to boost their attractiveness, one ground seems vaguely universal—the perception of scars. Burn victims face a whole different reality, where their scars are far more extensive and noticeable. Burn injury establishes the second most regular reason for trauma-related morbidity (Goel & Shrivastava, 2010). Cutaneous scarring present in second to third-degree burns can cause predicaments that deal with an individual's self-esteem as well as their re-integration to society (Amini-Nik, Jeschke, & Yousuf, 2017).

As advancements in medicine arise, there is an increase in the survival rate of burn victims (Patterson & Wiechman, 2004). Patients pose a reduced quality of life along with the psychosocial burden of scars that instigates depression, anxiety, sleep disturbances, and disorientation. To understand wound healing clearer, it is known that collagen leads a significant part in the arrangement of extracellular network (ECM) and improvement/relocation of cells and

tissues (Zhang, Yin, & Qe, 2020). Here, we discuss the collagen-rich Nile Tilapia skin (Oreochromis niloticus) and its potential role in burn treatment.

Objectives:

The purpose of this study is to assess the psychological influence of burns, the willingness of individuals to receive proper intervention for scar-reduction as part of their wound healing management, and to gauge their compliance on the application of collagen-hydrogels comprised of the Nile Tilapia skin as part of their treatment. It is in our goal to re-instate why appropriate wound healing should not consist primarily towards accelerated recovery but also minimal scar-formation. We aim to contribute to literature by depicting the psychosocial impact of scars and to incite awareness on the current treatment modality available for burn treatment—the collagen hydrogels of the Nile Tilapia.

Literature Review:

Psychosocial Impact of Burn Injury:

Victims of burn wounds face a plethora of issues that range from acute pain to suicidal ideations. Psychological parts of burn injury have been explored in various places of the world (Aggrawal, Dalal, & Saha, 2010). The cognitive ramifications of burn injury have been widely underestimated and wholly ignored. There seems to be a common ground for manifestations of body image dissatisfactions, PTSD, and depression (Lawrence, Heinberg, & Roca, 1998). These psychological distress symptoms have a short- and long-term impact on health, function, and quality of life (Patterson & Wiechman, 2004).

Subsequently, as mental health deteriorates due to low perceived self-esteem, many burn victims are left in a quagmire. Many scars that result from burns are inevitable as they are directly dependent on the depth of the wound. Excluding first-degree burns, both second and third-degree burns heal by scarring (Goel & Shrivastava, 2010). These marks can only be lessened by means of plastic surgery or other physical therapy measures and cannot be eradicated completely.

Brief Description of Burn Injuries:

In the wake of a cutaneous burn wound, there is the presence of collagen deposition following the healing of a scar that is less pliable than the uninjured adjacent skin (Amini-Nik, Jeschke, & Yousuf, 2017). The outcomes of this scarring are: hypertrophic and/or keloid scars. The most favorable outcome of scarring would be reduced discoloration with no extrusions and increased flexibility of the wounded area. To achieve optimal patient recovery, it is pivotal to reduce post-burn scars (Amini-Nik, Jeschke, & Yousuf, 2017).

Scars that are hypertrophic appear to be elevated, red, and within the parameters of the wound. They appear within 1-2 months of the initial injury. However, keloids develop months and years after the injury and exceed the confinements of the wound (Amini-Nik, Jeschke, & Yousuf, 2017). There are 4 stages of wound healing, which respectively consist of: (1) hemostasis, (2) inflammation, (3) proliferation, and (4) remodeling. These phases correspond to activation of several key signaling pathways; these include Wnt/ β-catenin, growth factor/cytokine pathways such as TGF- β pathway, Notch, and Sonic hedgehog (Amini-Nik, Jeschke, & Yousuf, 2017).

The Role of Collagen in Wound Healing:

On the aforementioned phases of wound healing, collagen plays a crucial role at each phase. Collagen constitutes majority of the extracellular matrix (ECM), and is the most abundant protein in animals (Harding, Leaper, & Rangaraj, 2011). The influence of collagen expands to: wound contraction, cellular differentiation, angiogenesis, cellular migration, platelet aggregation, and the induction of growth factors and cytokines (Harding, Leaper, & Rangaraj, 2011). The use of collagen dressings is alluring due to their properties in inducing maintenance of the chemical and thermostatic microenvironment of the wound, to deactivate or inhibit matrix metalloproteinases which are responsible for collagen degradation, and to maximize fibroblast production (Burton et al, 1978; Doillon et al, 1984, 1986, 1988; Palmieri, 1992; Brett, 2008).

Nile Tilapia Skin (Oreochromis niloticus) Collagen Hydrogels for Wound Dressings:

Most commercially produced collagen dressings are comprised of pig skin or bovine tendons. Yet, they pose the risk of potential contamination through foot and mouth disease, bovine sponge encephalopathy, and transmissible spongiform encephalopathy. This makes invertebrate or marine animals a viable choice for collagen. The Nile Tilapia fish skin constitutes of more than 40% of collagen in dry weight (Zhang, Yin, & Qe, 2020). Tilapia skin has non-infectious microorganisms, high measures of type I collagen, and comparative morphological composition to human skin, so it has been proposed as a possible xenograft for the administration of burn injury (Lima et al., 2019).

In a study conducted by Lima et al. (2019), the Nile tilapia fish skin was exposed to a thorough interaction of compound disinfection, glycerolization and light, trailed by microbiological tests for microorganisms and parasites, before stored in refrigerated sterile bundling. Before its utilization in the patient, the skin was washed in clean 0.9% saline for 5 minutes, with this interaction being rehashed multiple times in succession (Lima et al., 2019). According to Lima et al., “Tilapia skin was applied to the lesions, leading to complete reepithelialization within 12 and 17 days of treatment, respectively. No dressing changes were needed and no side effects were observed.”

Research framework:

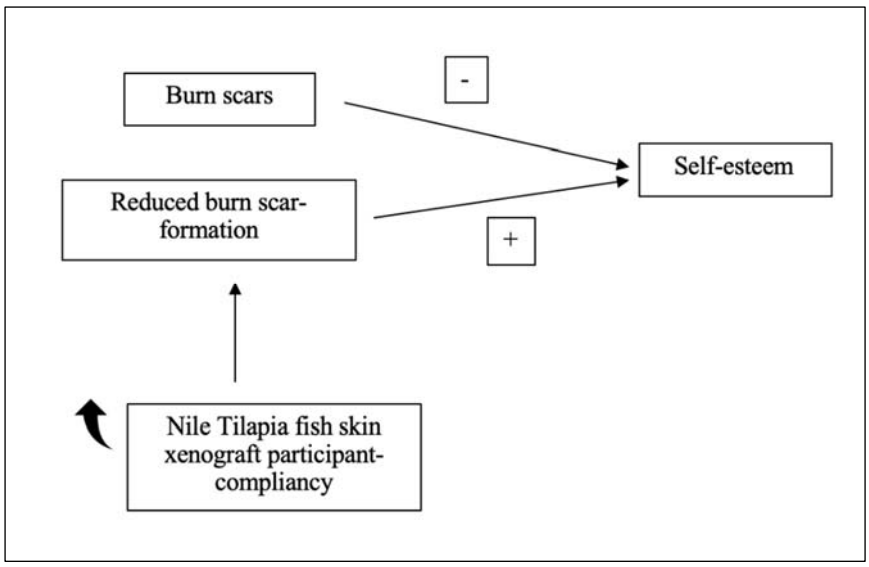

Figure 1. The figure above based on our hypotheses depicts a negative impact of burn scars on self-esteem, a positive impact on self-esteem due to reduced burn scar-formation, and an increased compliancy of participants opting for NTFS (Nile Tilapia Fish Skin) xenografts that promises reduced burn scar-formation.

Research hypotheses:

Most participants will have scars that do affect their self-esteem.

Majority of the participants would want to reduce the appearance of their scars.

Majority of the participants would prefer minimal-scar formation procedures as part of their burn wounds therapy.

Most participants will be open to innovative techniques to reduce scar-formation.

Most participants who will face a second or third-degree burn would be willing to have Nile Tilapia fish xenografts as part of their wound healing process.

Methodology:

Participants:

Surveys were distributed using the convenient sampling method through social media platforms such as Instagram, Facebook, LINE, WhatsApp, etc. A total of 101 responses were collected, from which only 99 were fully completed. The participants consisted of 57 females (56.4%), 41

males (40.6%), and 3 who preferred not to say (3.0%). Age and location demographics were not taken into consideration.

Measures:

- Experiencing a burn. Participants were asked to indicate whether or not they have burnt themselves before.
- Severity of the burn. If burnt, participants were asked to rate their burns as first, second, or third-degree burns.
- Hospitalization due to burns. Participants were asked whether or not they have been hospitalized due to their burns.
- Effect of burn-scars on self-esteem. Participants who have been previously burnt were asked whether or not their burn-scars affected their self-esteem.
- Reduction of scars. Participants were asked whether or not they would like to reduce the presence of any scars.
- Having the option of minimal scar-formation along their wound healing process. Participants were asked if they would or would not prefer having reduced scar formation as part of their burn wound recovery process.
- Being open to innovative scar-reducing techniques. Participants were asked if they would be open to try innovative techniques that could reduce scar-formation.
- Willingness to apply NTFS xenograft to reduce potential second or third-degree burn injury scar. Participants were asked whether or not they would be willing to apply fish skin to reduce scarring if they potentially had a burn injury.
- Personal reflection on scars. Participants were given an open-ended question on their outlook of scars.

Procedure:

The URL link of the finalized survey was distributed using convenience sampling through social media platforms such as Instagram, Facebook, Line, WhatsApp, etc. In the beginning of the survey, participants were informed of its purpose and the anonymity of the responses; they were also thanked in advance for their participation. The survey took approximately 5-8 minutes to complete, and was roughly available for 2 weeks before conducting data analysis.

Results:

- Experiencing a burn. 67 participants had experienced a burn (66.3%) and 34 participants had not (33.7%).
- Severity of the burn. 41 participants have had first-degree burns (41.4%), 26 had second-degree burns (26.3%), and 32 participants never experienced any burns (32.3%).
- Hospitalization due to burns. 87 participants had never been hospitalized for their burns (87.9%) and 12 participants had (12.1%).
- Effect of burn-scars on self-esteem. 65 participants responded that scars do not affect their self-esteem (66.3%) and 33 participants said they did (33.7%).

- Reduction of scars. 43 participants responded no (43.4%), 39 responded yes (39.4%), and 17 responded not sure (17.2%).
- Having the option of minimal scar-formation along their wound healing process. 60 participants responded yes (60.6%), 7 responded no (7.1%), and 32 responded maybe (32.2%).
- Being open to innovative scar-reducing techniques. 78 participants responded yes (78.8%), and 21 responded no (21.2%).
- Willingness to apply NTFS xenograft to reduce potential second or third-degree burn injury scar. 62 participants responded yes (62.6%), and 37 responded no (37.4%).
- Personal reflection on scars. Most participants had mixed responses of scars as a positive, negative, or neutral outlook on their self-esteem.

Discussion:

According to our small research conducted, majority of the participants do not correlate burn-scars as a hit to their self-esteem. 39.4% of the participants would not like to reduce their scars. However, 60.6% of the sample would like to have the option of minimal scar-formation as part of their wound healing therapy. 62.6% of the sample are open to using NTFS xenografts in the future for their potential burn injuries.

Conclusion:

Through this, we conclude, that although scars do not predominately affect our research sample's self-esteem in this study, we forgot to factor in ethnicity, geography, literacy, and age into our study, which does not give us a clearer understanding and a good sample size. However, it must be taken into consideration, that most participants are eager to have minimal-scars and the subsequent procedures involved as a part of their wound healing management. They are open and willing to use Nile Tilapia fish skin as a potential treatment for their future burn wounds. We have succeeded in spreading awareness of NTFS as a potential treatment for burn wounds and do believe that certain incentives in the healthcare system must be taken to include minimal-scar formation as part of wound recovery.

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Chiari network through the years (1563-2020) – should we worry? A chronological review

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Abstract: The Chiari network is an anomaly of the heart, believed to be embryologic remnant and anatomic variation. The Chiari network has gone a long way since firstly noticed in 1563, slowly the importance of these fibers, extending from the ostium of the inferior vena cava to the region around crista terminalis, have gained their place as a structure that should be recognized. Because it is believed that the Chiari network is a rare finding, it could sometimes be neglected or even missed and this could potentially lead to complications and so that knowing the importance of this structure is crucial. Different pieces of information and case reports have been published through the years, regarding the association of the Chiari network with other heart anomalies like atrial septal defects, atrial septal aneurysm and with the possibility of being a place predisposing for thrombus formation. While, other reports state that the network could act as a filter for thrombi. Regardless the difference in some reports, the connection of the Chiari network with some pathologies and possible complications is strong and should rase attention. The aim of this chronological review is to present the available published information regarding the Chiari network and to highlight the most important clinical findings, that could be beneficial for physicians.

Key words: Chiari network, heart, complication, thrombus, chronological review

Introduction:

The Chiari network is an anomaly of the heart, believed to be embryologic remnant and anatomic variation. [1,2] Chiari network was founded and firstly described by Hans Chiari, Australian pathologist, who was born in Vienna, on November 4, 1851. His enormous contribution to today's medicine is indisputable. Describing the Chiari malformation and the Budd–Chiari syndrome in 19th century he contributed to the base of the todays pathology of the nervous system. Not only that, but in 1897 he documented the findings of von Rokitansky in 1875, regarding the network of fine fibers extending from the ostium of the inferior vena cava to the Tubercle of Lower in the heart, giving them the eponym Chiari's network. [2,3] In his work from 1897, Chiari reported eleven cases with this finding and he thought that it was remnant of the right venous valve of the septum spurium. [4] Through the years the Chiari network has been coming to the attention of physicians in different ways, a lot of case reports regarding the connection of the Chiari network with other heart anomalies and pathologies, but on the other hand some articles stated the possible benefit of the network in the right atrium. The chronological review presents the information available regarding the Chiari network from 1563 to 2020 and highlights the important aspects and believes through the years. We believe that

knowing the full information and possible outcomes for patients with Chiari network is the key for preventing and lowering the complications rate.

1563 – 1960:

Since, firstly being described, interest in the so-called Chiari network has been raising. With the years several case reports about possible pathologies associated with the Chiari network and some cases, reporting otherwise have been published. Interestingly enough, the first writing about Chiari's network was back in 1563, when Eustachius described the structure variations in the valve of the inferior vena cava. In 1875, 312 years later, Rokitansky described this structure in his single case report of an intermittent membrane extending over the ostium of the inferior vena cava in an individual. The next year (1876) when examining a hundred hearts, Lauenstein found five in which the valve of the inferior vena cava was formed by a continuous web of tissue. After that in 1897, Chiari again, described and reported 11 cases with these findings and from that moment on, these variations were called Chiari's network. Also, he suggested that this network could act as a filter for thrombi, that come from the inferior vena cava and can potentially end up in the lung. In 1929 there was a report, which found 11 cases of Chiari network in 120 hearts and it was stated that this large network could be a place for thrombus formation, rather than a filter, as Chiari supposed. [2,4,5] Research by Ferdinand C. Helwig in 1932, reported eight autopsy cases of Chiari's network. In his study, the network had no clinical significance and the author stated that if more care is provided in removing and opening of the heart, these structures will be found more often, since they are easily destroyed in the process. [5] According to Wright et al., in 1948 who examined 512 specimens, a true Chiari network was apparent in only one heart, even though 9 specimens (1,9%) of all 512 had fibrous cords over the orifice of vena cava inferior. The one heart in which these fibrous cords were attached to the crista terminalis, fulfilled the requirements from Hans Chiari, in order to set as Chiari's network and the other 9 hearts had cords attaching to the edge of the valve. [6] G. Austin Gresham (1956) found network like structures in 57 adult hearts of 260 studied. He reported that these structures contain cardiac muscle and may provide an alternative path for the passage of the impulses. In one of the cases in the study, the person was reported to have variation in his P-R interval, which according to Gresham could be associated with conduction via the Chiari network, which provides an alternative path for conduction of impulses from sinu-atrial node to the ventricle. [7] Research by Powell and Mullaney (1960) found fenestrations of the Eustachian valve in 24 out of 100 hearts. In some of the cases the valve was represented by fibers, which were with widespread attachments and in 12 cases there was a tissue connection between Eustachian and Thebesian valves. According to their research, Powell and Mullaney believe that these fibers in the right atrium can potentially lead to thrombus formation, especially when there is atrial fibrillation. If the network is presented by fenestrations, it could remove emboli, but this scenario is not that likely to happen and it will be by chance. [4] In these early years, investigations were based on autopsies, where the net like structures of Chiari network could easily be destroyed and neglected. Every piece of information in that time was valuable, but the finding of a cardiac muscles in Chiari network, marked the possible clinical importance of this structure.

1961 – 1990:

In 1972, Goldschlager et al., reported an interesting case associated with Chiari network. During a catheterization from right basilic vein in patient with a secundum atrial septal defect, upon extraction of the catheter, it got trapped and looped at the level of the atrial septal defect. At

thoracotomy, the tip of the catheter was curled upon itself and was entrapped in the strands of Chiari network in the atrial septal defect. In the presence of Chiari network and an atrial septal defect, the network can be found anywhere within the defect and therefor cause trouble in the process of right heart catheterization. Even though, this is rarely seen, caution should be placed on careful evaluation of the patient prior to catheterization. [8] The evaluation method on which we can rely on is echocardiography, because of its wide usage, fast and easy interpretation. The value and the accuracy of the ultrasound method are appreciated and echocardiography is a key part in the process of evaluation of the patient. Werner et al., first described the transthoracic echocardiographic appearance of the Chiari network in 1981. They found it in 19 of 1248 patients (1,5%), the finding is important, because the widely mobile appearance in the right atrium, could be mistaken with vegetation, right-heart thrombus, tumor or flail tricuspid leaflet and careful evaluation with different acoustic windows, tomographic views and even an intravenous contrast material, which will outline the course of the inferior vena cava is important for ruling out other possible pathologies. [9] Benbow et al., (1987) described a case of a patient with massive right atrial thrombus formed on a Chiari network. The patient had acute myeloid leukemia, which was treated with cytotoxic chemotherapy via Hickman catheter, which maybe contributed to the complication. On necropsy and histological examination, they founded a big yellow mass in the right atrium, which was thrombus without infection. After removing the thrombus from the atrium, inferiorly there was a membranous and partly reticular structure stretched across the atrium. The network of fibers was connecting the Eustachian and Thebesian valves, containing large spaces between the stands, which did not result in some form of obstruction to the blood flow, until there was a thrombus formed. The finding is typical Chiari network with supervening thrombosis. [10] These years marked the important role of echocardiography in the heart examination and the first procedure complication with catheter entrapment in Chiari network was published.

1990 – 2000:

In 1990, Goedde et al., published a case of a 69-year-old patient with sudden onset of palpitations and dyspnea. On the day of the admission, there was nothing remarkable on the echocardiographic investigation, but 3 weeks later on a follow-up a gelatinous-looking mass was noted in the right atrium, finding associated with atrial thrombus. Surgical intervention in order to remove it was the chosen method. A thrombus was enmeshed into the Chiari network, showing that this anomaly in the right atrium played a role of a congenital inferior vena cava filter by preventing a massive pulmonary embolism in this patient. [11] Two years later in 1992, Wasdahl et al., presented a case of a Chiari network with attached gray-white papillary mass, founded at necropsy. The structure was fibroelastic papilloma, arising from Chiari network. Most of the cases (80%) fibroelastic papillomas occur on heart valves, but with this finding, they are added to the list of differential diagnosis of intracardiac mass in the right atrium, near the ostium of the inferior vena cava. [12] After another two years in 1994, Edwards et al., reported a case of a patient with multiple ischemic strokes caused by emboli coming from a thrombus on a Chiari network. This patient had a Chiari network and a patent foramen ovale with right to left shunt through it. When a transesophageal echocardiography was done, it was clear that the network of fibers in the right atrium with small noduli, was moving freely. Since, the noduli on the Chiari network, disappeared after an anticoagulation for six months, the authors stated that this structure was the origin of the emboli, which caused the ischemic strokes. Even more, according to them transesophageal echocardiography is superior to transthoracic in the process of diagnosing

cerebrovascular incidence from unknown origin. [13] The place and the importance of transesophageal echocardiography was reported in another study from Schneider et al., (1995). They found that the prevalence of Chiari network was 2% (29 of 1436 patients) and in 23 of them the transesophageal echocardiography was done because of the suspected cerebral embolism. Proving the superiority of transesophageal echocardiography to transthoracic is that in only 8 of these 29 patients the Chiari network was visible in transthoracic echocardiography. According to the study, 23 of the 29 patients (79%) with Chiari network had a large Eustachian valve and 24 of the 29 (83%) had a patent foramen ovale. Even more, 24% of the patients with Chiari network had an atrial septal aneurysm. In none of the 29 patients with Chiari network was thrombus found, however the authors believe that the presence of Chiari network can lead to maintaining an embryonic flow pattern in the right atrium by directing the blood towards the region of fossa ovalis, which can cause a persistence of the foramen ovale, atrial septal aneurysm and may favor a paradoxic embolism. [14] A few years later, El-Khouri et al., (1998) reported an unusual case of a 3-days-old infant born at 27 weeks gestation from a mother which developed eclampsia and was status post liver transplantation. On echocardiography examination, a prominent Chiari network, floating freely in and out of the right ventricle was observed. Three days later, the same Chiari network was moving through the patent foramen ovale, in and out of the left atrium, causing the fibers to get trapped in the patent foramen ovale. [15] The next year in 1999, Cooke et al., presented a 72-year-old patient admitted for percutaneous closure of an atrial septal defect. Upon evaluation a prominent Chiari network was observed, which later was the place where the catheter tip got tangled and pulled part of the Chiari network with it in the left atrium. The herniation was returned fully to the right atrium by withdrawing the catheter from the left to the right atrium. Using transesophageal echocardiography, during the whole procedure lead to successful deployment of the closure device across the atrial septal defect. This case highlights the importance of transesophageal echocardiography in the atrial septal defect closure procedure and the careful catheterization in the presence of Chiari network. [16] The progress regarding the Chiari network for only 10 years, between 1990 – 2000 was remarkable. Transesophageal echocardiography took its place as a method of choice for exact evaluation of the Chiari network. Again, second report of a catheter entanglement into Chiari network was published and in another article the possibility of association between thrombus formation and the network was raised. Key findings were the high prevalence of Chiari network with atrial septal defect and atrial aneurysms, which may predispose to more complications like paradoxic embolism. Important finding was also that Chiari network, could be a place for the formation of fibroelastic papillomas.

2001 – 2010:

In 2001, Shimoike et al., presented a case similar to the one in 1999. In their patient, who had idiopathic right ventricular outflow tract tachycardia, they had to do an electrophysiologic study and a radiofrequency catheter ablation. The patient had a Chiari network, noted prior to the procedure with a transthoracic echocardiography. In the process of the procedure, when the catheter was introduced into the right atrium, the tip of the catheter got entrapped by the Chiari network. They successfully released it by delivering radiofrequency energy for 4s. This was the first reported case of a guidewire becoming entrapped by the Chiari network. [17] Payne et al., (2003) published the first case of an infectious endocarditis developed solely within a Chiari network. The patient was described to have highly mobile right atrial mass on transesophageal echocardiography and then intraoperative exploration prove that the mass is connected to the

Chiari network. The case presented, highlights Chiari network as a place for developing infectious endocarditis and it should be considered in differential diagnosis of endocarditis. [18] Very interesting material of three consecutive patients with abnormal interatrial conduction was published by Prajapat et al., (2007). They report for the first time an interatrial block (P-waves ≥ 110 ms) in three patients with Chiari network in right atrium. The widened P-wave duration is believed to be a predictor for atrial fibrillation and even though the Chiari network is not proved to be involved in the interatrial block, it is believed that an accessory pathway in the right atrium, may produce prolonged P-waves on the electrocardiogram. [19] Reports in the past have shown that there is a possibility of a conduction through the Chiari network, since these structures contain cardiac muscle cells. [7] Five years after the report of infectious endocarditis associated with Chiari network, Mousavi et al., published similar case of a patient with infectious endocarditis, presented by a large mobile vegetation in the right atrium attached to the Chiari network. Although, this was the second reported case of an infectious endocarditis associated with Chiari network, this structure could be a place for bacterial invasion or could be secondarily seeded be tricuspid valve endocarditis. [20] In the same year, another article was published by Latif et al., (2008) presenting a case of a patient with mobile mass attached to the Chiari network in the right atrium, visible on transthoracic echocardiography, without any vegetations on it or on the valves. They presumed that the mass was a possible source of infection, since the clinical and laboratory findings were showing typical signs of infection and they started the patient on intravenous antibiotic. Since, the continued presence of the mass, even after the treatment, the patient underwent surgery and the histological examination of the removed mass showed an infective endocarditis of a papillary fibroelastoma on Chiari network of right atrium. With this case, it is proved that Chiari network could be a potential place for infectious endocarditis and fibroelastoma. Also, a papillary fibroelastoma on a Chiari network, could alone be a source of infectious endocarditis. [21] Another unusual case published in 2008 is by Shakur et al., reports a patient with platypnea orthodeoxia, having an atrial septal defect, rigid, hypertrophied septum and an extensive mobile Chiari network, moving dynamically with posture. The authors believe that the late emergence of platypnea orthodeoxia is due to the Chiari network in someone with lipomatous changed, hypertrophied atrial septum. [22] Teo et al., (2010) published an interesting case of difficult administration of a retrograde cardioplegia through a cannula inserted into the coronary sinus. The tip of the cannula was entangled by fibers of the Chiari network, causing difficult advancement of the cannula into the coronary sinus. They successfully inserted the cannula by withdrawing and rotating the tip. The use of transesophageal echocardiography is appropriate in situation like this, resulting in atraumatic and precise cannula placement. [23] In the begging of the 20th century, the first case of an infectious endocarditis of the Chiari network was published, followed by another two similar cases, one of which a combination of endocarditis and papilloma of the Chiari network. Once again, attention was placed on the possible entrapment of a catheter into the Chiari network during electrophysiologic procedures. The association between the presence of a Chiari network and interatrial block was considered.

2011 – 2020:

In 2011, a case report from Ko et al., presented an 11-day-old boy with oxygen saturation of 70% and persistent lip cyanosis, since birth. Upon medical examination the transthoracic echocardiography showed a patent foramen ovale and a freely mobile structure extending from the border of the inferior vena cava to the superior of the right atrium. This structure was a highly mobile Chiari network moving in and out of the tricuspid orifice during systolic and

diastolic phases. [24] Case like this are rare, but as presented earlier in the review, another similar case was published in 1998. [15] Aydın et al., (2011) presented a case of catheter entrapment during procedure for atrial septal defect closure. After deploying and pulling backwards the catheter got entrapped in the Chiari network, successful removing was achieved by forceful traction. The case, again presents that a Chiari network could be problematic during percutaneous atrial septal defect closure procedures. [25] A year later in 2012, Obaji et al., reported an interesting case of a patient with polycythemia vera and Chiari network. The presence of a thrombus within the Chiari network was proved with transesophageal echocardiography, which was treated successfully with warfarin. In this case, the authors believe that the Chiari network served as a protective intrinsic filter in the prevention of massive pulmonary embolism. [26] From 2015 until nowadays there have been many papers published about entrapment of a catheter or a guide wire into the Chiari network, following percutaneous intracardiac procedures. Hightower et al., (2015) report a case of a guide wire entanglement in the Chiari network in patient undergoing a routine chest port placement. Transesophageal echocardiography was used by the team in order to visualize the guide wire and then, they forcefully removed it. The patient was stable and asymptomatic, during the procedure. [27] Similarly in 2016, Aung et al., published a case of a pacing lead entanglement in the Chiari network, treated with laser sheath removal, using intracardiac echocardiographic identification. [28] Two years later, Abdelrahman et al., reported a case of a Lasso catheter that got entrapped in Chiari network, successful extraction was done by internal jugular venous access. In this case, even though the complication, the patient did well and was stable. [29] Nagahama et al., (2019) also report a case of a catheter tip trapped in the Chiari network and this was the first published case we found in which after entrapment the patient had problems. According to the article by Nagahama et al., their patient had severe right hypochondrium pain during traction of the catheter. They successfully removed the catheter tip by applying radio-frequency energy at entrapment site and despite of the pain in the process of the procedure, the patient had no other complications. [30] In 2020, Quininir et al., also describe a case of a catheter entrapment into Chiari network, during catheter ablation procedure, they removed it by advancing the sheath over the tip of the catheter. Part of the Chiari network was entangled in the splines after removing. [31] Even though the last ten years of progress in studying the Chiari network were mainly associated with catheters and guide wires entrapment, a couple different and unusual cases were published, too. In 2016, Schwimmer-Okike et al., reported an interesting case of a donor for an Anatomy dissection course, which appeared to have a net like structure in the right atrium of the heart, discovered by students. The microscopic and histologic findings were consistent with the Chiari network, but another interesting element was that a thrombus on the network was found. The person had atrial fibrillation and a stroke episode, because of that the authors believe that the presence of the Chiari network is the possible cause for the atrial fibrillation and the stroke, leading to the death of the person. [32] Another interesting article was published by Irdem et al., (2020) concerning the association between P-wave changes and Chiari network. In their study they found that in patients with Chiari network, the P-wave duration and P dispersion were increased and these markers are the most important for accessing the risk atrial arrhythmia and atrial fibrillation. [33] In the last ten years, more and more reports of catheter and guide wire entrapment in Chiari network have been published. We believe that this is caused by the broaden indications for electrophysiological procedures in the last years and with more interventions, the complication rate could go higher. Even though, this is considered a rare complication, it should always raise attention when a patient with Chiari network is entering the electrophysiological or

catheterization laboratory. We believe that the association between electrophysiological procedure complications associated with the Chiari network is valuable the detailed evaluation of the patient prior to the procedure is crucial for preventing possible periprocedural difficulties.

Conclusion:

The Chiari network has gone a long way since firstly noticed in 1563, slowly the importance of these fibers, extending from the ostium of the inferior vena cava to the region around crista terminalis, have gained their place as a structure that should be recognized. Even though, a rare finding, Chiari network is associated with other heart anomalies like atrial septal defect, atrial septal aneurysm or large Eustachian valve, which in turn can lead to lethal complications. Chiari network, could be a structure predisposing to catheter or guide wire entrapment, bacterial colonizing, fibroelastic papilloma or thrombus formation, but on the other hand there are reports presenting the Chiari network as an internal filter for thrombi. Keeping in mind all of the information and case reports published through the years, the Chiari network should be something that we keep in mind, when evaluating a patient and even more attention in seeking it, should be placed for patients referring for electrophysiological procedures, in order to prevent possible intraprocedural complications.

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Side Effects of COVID Vaccine

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Abstract

The world is in the midst of Covid-19 pandemic, and after so much research effective vaccines of Covid have rolled out and now more than 820 million Covid vaccine doses have been administered all over the world. Vaccines save millions of lives each year and they work by training and preparing the immune system of the body and to fight off viruses and bacteria they target. After vaccination, if body again encounters to those viruses or bacteria, the body is immediately ready to destroy them and prevent the illness. Covid vaccine also work the same way but many cases of side effects of Covid vaccine are emerging from many parts of the world. Vaccines that are the subject of debate are Pfizer-BioNTech, Moderna, AstraZeneca, Johnson & Johnson and Covaxin. The most common post-vaccination symptoms found are fever, headache, muscle pain, etc. The risk of getting blood clot is also found most commonly in females. Vaccine also causes irregular periods and heavy menstrual bleeding in females.

A cross-sectional online survey was done which included questions to study the post-vaccination experience.

From the research that we conducted, we were able to observe that middle aged people are suffering more post-vaccination symptoms than older people. Further, females were observed to have severe side effects than males, also some females faced irregular bleeding and heavy menstrual bleeding (25%). Almost half the respondents had pain in the area of injection (54%). Three most common post-vaccination symptoms that reported were headache (64%), fever (60%) and muscle pain (46%). Some respondents (22%) took pain killers due to certain pain after vaccination, which is not advisable as it interferes with the action of vaccine. Respondents also reported blurred vision (12%), fainting (4%), pain in epigastric area (16%), pain in leg (12%) which are the symptoms of developing blood clot. Respondents who drink or smoke are also found. Alcohol makes the vaccine little ineffective as well as it reduces the immunity of the individual.

Younger adult are getting more post-vaccination symptoms from which females are more sensitive to the vaccine as they are suffering more severe symptoms and are more prone to develop blood clot. Common post-vaccination symptoms are fever, headache, muscle pain, etc.

Post-vaccination symptoms of Covid vaccine are very natural to happen and because of these side effects one should not avoid receiving the vaccine.

Introduction

As the body is building immunity against virus by activating T and B lymphocytes that recognize the virus and produce antibodies against virus respectively, it is very normal for an individual to experience side effects. The most common post-vaccination symptoms that people are encountering are mild-to-moderate. These can be-headache, fever, joint pain, muscle pain, nausea, fatigue, chills, etc. Many individuals reported pain and some irritation on the site of vaccine injection. The irritation can be in the form of swelling, redness and itchy rash. These common side effects are not unexpected and lasts only for a few days. It is noted that death occurred in cases where the person had diabetes, hypertension or any other chronic disease.

A person can face allergic reaction to certain ingredients in the vaccine. People having allergy to one or more ingredients may suffer respiratory symptoms, skin rash, swelling, etc. It is advised that people who suffered allergic reactions in the first dose of vaccine should not go for the second dose. There are rare cases of anaphylaxis that is i.e. severe and potential life threatening allergic reaction. A person having anaphylaxis may involve symptoms like nausea, low blood pressure or shortness of breath.

The vaccine has also reported cases of blood clots along with thrombocytopenia which is a type of immune response. Rare cases of cerebral venous sinus thrombosis that is blood clot in the brain also occurred. Some symptoms that occur due to thromboembolism were- abdominal pain, leg pain, leg swelling at the end of the day, shortness of breath, fainting, loss of control and blurred vision.

Post-vaccination symptoms were more prominent in women than men. Reproductive hormones such as estrogen and testosterone may have an important role in this difference in the reaction to the vaccine. It was found that estrogen causes body to produce more antibodies to the vaccine, thus leading to a higher immune response. Some women also suffered irregular bleeding and heavy menstrual flow during periods.

Literature review

Covid vaccine is now getting available in several parts of the world. However, their positive effects and negative effects are still the subject of discussion. Currently, 13 Covid vaccines have been authorized for use in various parts of the world (World Health Organization, 2020)

Name	Manufacturer
BNT162b2	Pfizer-BioNTech
mRNA-1273	Moderna

Ad26.COV2.S	Janssen (Johnson & Johnson)
AZD1222	Oxford-AstraZeneca
Covishield	Serum Institute of India
Ad5-nCov	CanSino
Sputnik V	Gamaleya
Covaxin	Bharat Biotech
BBBIBP-CorV	Sinopharm
Inactivated (Vero Cell)	Sinopharm
CoronaVac	Sinovac
RBD-dimer	Anhui Zhifei Longcom
EpiVacCororna	FBRI

Except the vaccine produced by Johnson & Johnson all other vaccines are given in 2 doses, Johnson & Johnson vaccine is given in 1 dose.

Since many Covid vaccines have come in the world, millions have already received their vaccine shots. But many post vaccination side-effects were experienced by vaccinated individuals which have raised many eyebrows (U.S. Food and Drug administration, 2020).

Common side effects on the arm where vaccination shot is given are pain, redness and swelling. Fever, chills, headache, nausea, joint pain, muscle pain and fatigue are some of the other common side effects of vaccination which are the signs that body is building protection. These side effects are seen because our immune system orders our body to react in different ways. It increases the body temperature to kill the virus, also it increases the blood flow, so more immune cells get circulated in the body. Side effects after second dose may be more intense than the ones experienced after first shot. (Centers for Disease Control and Prevention, 2021)

Common side effects shows that vaccine is working properly and producing antibodies. And if there are no side effects this means that vaccine is not effective. Most of the common side effects go away in few days on their own and it could also be possible that any individual would not have any side effects. However, if individuals experience severe reactions, then they should seek medical help. To reduce pain and discomfort on the area where vaccination was given a clean,

cool, wet washcloth should be applied over that area and exercise of the arm should be done. After receiving the vaccine the person is asked to stay at vaccination site for 15-30 minutes to observe any immediate reactions of the vaccine. According to the guidelines by the Ministry of Health and Family Welfare, antibodies develop after two weeks of receiving second dose (Saleh, E., Moody, M., & Walter, E., 2016).

According to WHO, a severe allergic reaction (such as anaphylaxis) is a rare side effect of the vaccine. According to WHO the healthcare providers assess patient's medical history to determine if a patient is at risk for severe allergic reactions. Any pain killer should not be taken after vaccine dose as pain killer can interfere with vaccine and can make it ineffective (Polack, F., Thomas, S., Kitchin, N., et al., 2020)

The Covid vaccines have been shown to be effective in older adults, people age 50 and older experience fewer side effects than younger recipients. Only about 25 percent of people ages 50 to 64 and 4 percent of those ages 65 to 74 who received the Pfizer BioNTech or Moderna vaccine between December 14 and January 13 experienced side effects, according to CDC data. Meanwhile, 65 percent of those under 50 reported a reaction. Similar effect were showed in the clinical trial data from Johnson & Johnson vaccine. Researchers are still studying this case. Some researchers believe that its likely related to the declining immune response that comes with age.

Apart from the common side effects of the vaccine, some less common side effects have also been reported by women. In some women heavier and off-cycle periods than usual have been reported after Covid vaccine. The tracking system for side effects from the US centers for Disease control and Prevention (CDC) , which is known as the Vaccine Adverse Event Reporting System (VAERS) has till now received at least 32 reports of altered periods out of 56,000 participants who responded to the query. Although, this is a small percentage of the number, but it indicates that there is a link between missing period and Covid vaccine shot.

The research is still going on how Covid vaccine affects the menstrual cycle. But some experts believe that it could be because the vaccine stresses the immune system and the body may respond to these kinds of stresses by changing the menstrual cycle. As per experts, due to the presence of nanoparticles in the vaccine there could be change in the menstrual cycle. A temporary immune reaction can be created by these nanoparticles in some women that may kill some platelets and the platelets play an important role in clotting. These cells regenerate frequently so there is nothing to worry about, however, the changes could be witnessed during the menstrual cycle. The vaccine does not affect the fertility in any way (Fink, A., & Klein, S., 2018)

Covid vaccines are turning the tide but they are not without risks especially for women. There have been rare cases of blood clotting even fatal ones, leading some governments to slow down vaccinations. Denmark, Norway and Iceland paused use of Oxford-AstraZeneca Covid vaccine

as a precaution after reports of recipients developing blood clots. Pfizer, Moderna and Johnson & Johnson vaccines are also reported for developing blood clots and hence, their use is paused in several parts of the world. AstraZeneca vaccine has also been reported to develop thrombocytopenia (an abnormally low blood platelets).

The risk from dying Covid is much higher than getting a blood clot from a vaccine. But even more concerning is a new report from Oxford University that shows catching the coronavirus puts you at even more risk of a deadly blood clot. AstraZeneca vector vaccine was getting success in the UK's vaccination program, but from now on its use there will be restricted to those over 30 years of age. There have been worries in the European Union about its effectiveness and potential side effects. Germany initially restricted its use to under 65 years of age. Now Berlin is recommending it for over 60 years of age. Those worries were compounded by several cases of a rare thrombosis type following AstraZeneca vaccination, some of them fatal. Scientists have been investigating the reports and circumstances of the thrombosis.

Britain's Medicines and Health care regulator agency says 20 million doses of the AstraZeneca vaccine had been administered by end of March with 79 cases of thrombosis late reported, 19 of which were fatal. The cause is thought to be a rare immune reaction. Most of the, presented some two weeks after inoculation. There are no apparent risk groups such as age or sex. Several countries like Germany, France and Canada have tightened restrictions on the use of AstraZeneca's Covid vaccine. Others have suspended totally waiting for the EMA's verdict

Johnson & Johnson was the third vaccine in United States to get emergency-use authorization which was given at the end of February, beginning of March. Since that time about 6.8 million doses have been given in the United States and during that time there is reporting system called the VAERS, where they have been track of adverse reactions and during this time there have been about 6 patients that have developed Cerebral Venous Sinus Thrombosis (CVST). All the 6 patients were women between the age of 18-48, who developed this complications between 6 and 13 days post vaccination. One of them has died, the other one is in critical condition (Jennifer, S., Chen S., Alfajaro M., Ryan, D., Jin, W., Filler, R., Eisenbarth, S., & Wilen C., 2021).

Due to Covid vaccine blood clots can also develop in lungs, organs of abdomen or legs. If clot develops in lungs then there would be sensation of sensation of sudden shortness of breath. If clot is in abdomen there could be abdominal pain, epigastric pain. If it is in legs then there could be pain in legs, either on one side or on both, also there would be swelling particularly at the end of the day.

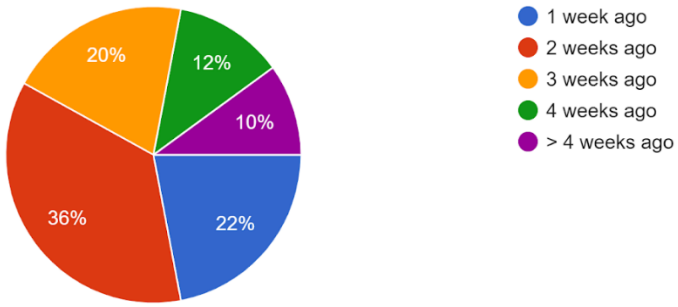
Methodology

An observational study was carried out quantitatively using a standard questionnaire on 50 persons through online survey to study the prevalence and nature of side effects of Covid vaccine in this population. The population was selected based on whether they received vaccine or not. Different side effects (pain at site of injection, fever, nausea, joint pain, fatigue, blurred vision, faintness, leg pain, heavy menstrual bleeding) in various groups (based on age, gender, how many weeks ago they received vaccine, whether they received one shots or both shots of vaccine) were compared using tables and pie-charts.

Results

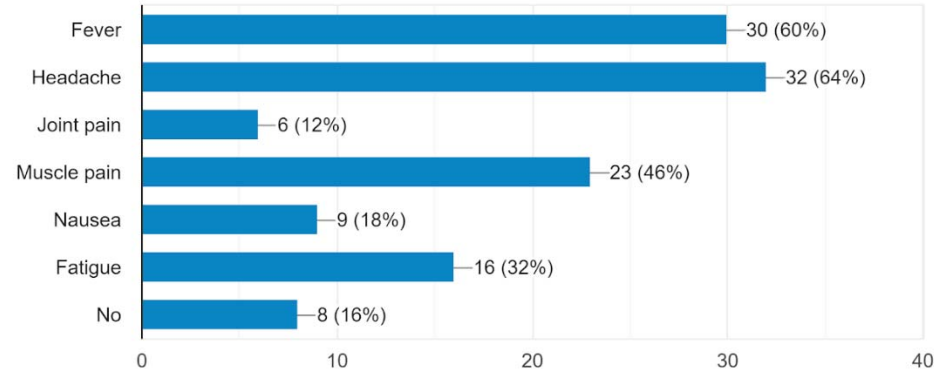
Total 50 persons responded to the survey from which 60% were male and 40 % were female. 56% of respondents were of age group 41-60 years, 30 % of respondents were of age group 18-40 years and 14 % were of age group more than 60 years.

36% of respondents received vaccine 2 weeks ago, 22% of respondents received vaccine 1 week ago, 20% of respondents received vaccine 3 weeks ago, 12% respondents received 4 weeks ago and 10% respondents received vaccine more than 4 weeks ago.



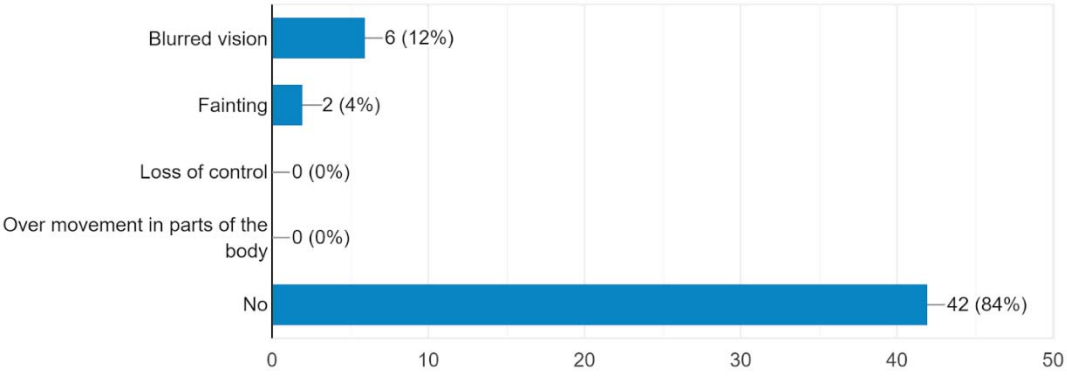
From the total respondents 50% had received both the shots and 50% had received only one shot. 46% of the total respondents felt pain at the site of injection.

Overall, 84% of the respondents reported at least one post vaccination symptom. Fever (60%), headache (64%), joint pain(12%), muscle pain (46%), nausea (18%), fatigue (32%) were the most common symptoms.



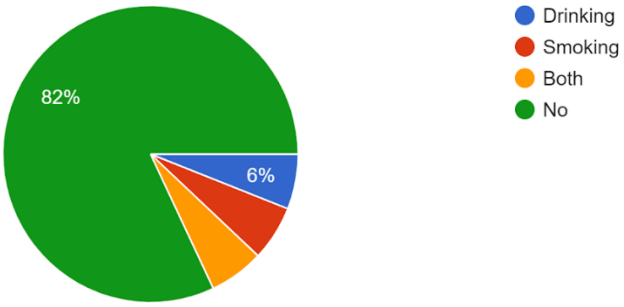
Only 14% respondents seek medical help after vaccination to relieve the severity of their symptoms. Allergic reactions were reported by 12% of the total respondents. 22% of the respondents took any pain killer after the vaccination. From the total number of female respondents, 25% reported irregular periods and heavy menstrual bleeding after the vaccination.

16% of the respondents reported at least one severe symptoms of getting blood clot.



Epigastric or abdomen pain was reported by 16% of respondents and pain in legs was reported by 12% of respondents. Swelling in legs is seen only in 4% of respondents and shortness of breath was faced by 12% of respondents. From the total respondents, 12% have diabetes, 10% have hypertension and 4% have both diabetes and hypertension.

Smoking is done by 6% of respondents, drinking is done by 6% of respondents and 6% of respondents do both drinking and smoking.



Discussion

Our study support a significant relation between gender and side effects of vaccine. Almost all women faced the side effects of the vaccine and some of them had faced severe symptoms that they seek medical help. Irregular periods and heavy menstrual bleeding was also reported 5 females. Most of the allergic reactions were seen in females. Severe symptoms like blurred vision and fainting were reported in 8 persons from which 4 were females and 4 were males. Leg pain was reported in 4 respondents.

In the age group of more than 60 years severe symptoms of getting blood clot like blurred vision was reported by only one respondent. Most of the severe symptoms of blood clot were reported in the age group of 41-60 years. The data of our research shows that people of age group 18-40 and 41-60 years are getting more post-vaccination symptoms as their immune system is more active and responding more to vaccine while people of age group more than 60 years have depressed immune system because of old age, hence their immune system is responding less to Covid vaccine. Most of the post-vaccination symptoms can be seen within 2 weeks of vaccination. The prevalence of post-vaccination symptoms is almost same after one first and second shot of vaccine. Most common post-vaccination symptoms are headache, fever, muscle pain, fatigue, nausea and joint pain. Pain at the site of injection is very common among the population. Half of the population had reported pain at the site of injection. Very less cases of allergic reactions were reported. 22% of respondents had taken pain killer after vaccination which relieved few of their symptoms, but it may interfere in the action of vaccine. A less proportion of population also faced epigastric or abdomen pain, leg pain and shortness of breath. Only 2 respondents reported for swelling in legs. A significant association was also found between population who drink or smoke and getting side effects. No significant association was found between chronic disease and severity of post-vaccination symptoms. One female respondent was also reported who may have chance of developing blood clot.

Conclusion

Most of the respondents that reported post vaccination symptoms were of age group 18-40 and 41-60 years from which females were reported to have more symptoms and they seek more

medical help to relieve the post-vaccination symptoms. The respondents who were vaccinated within 2 weeks had reported more symptoms. Headache, fever, muscle pain, etc. were the most common post-vaccinations symptoms. Irregular periods and heavy menstrual bleeding was reported by 25% of females. Severe symptoms were reported by 16% of respondents. Swelling in leg was reported by only 4% of respondents. No unusual symptoms were reported by respondents who had chronic disease.

Recommendations

Post-vaccination symptoms after receiving first or second dose of vaccine are not unexpected. So, to reduce pain and discomfort at the site of injection clean, cool and wet cloth can be applied or doing exercise of arm can also help. Discomfort from fever, headache or muscle pain can be relieved by drinking plenty of fluid. These symptoms relieves in few days. Taking any pain killer to reduce symptoms is strictly prohibited as it interferes in the action process of vaccine. Females should take more care of themselves because post-vaccination symptoms affect more severely in females and menstrual bleeding changes can also occur in females due to vaccine. Females have very high chance of getting blood clot than males. Hence, females are more sensitive to the vaccine. If any symptom of blood clot like blurred vision, fainting, pain in one or both legs, pain in epigastric area, shortness of breath, etc. is seen after the vaccination, immediately contact to the doctor. Despite the vaccine having so many side effects, it is advised to take the vaccination as its benefits are much higher than its risks.

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Annexes

Annex 1 (Questionnaire)

1. What is your age?
    - <18 years
    - 18-40 years
    - 40-60 years
    - >60 years
2. What is your gender?
    - Male
    - Female
    - Other
3. When did you receive your vaccine?
    - 1 week ago

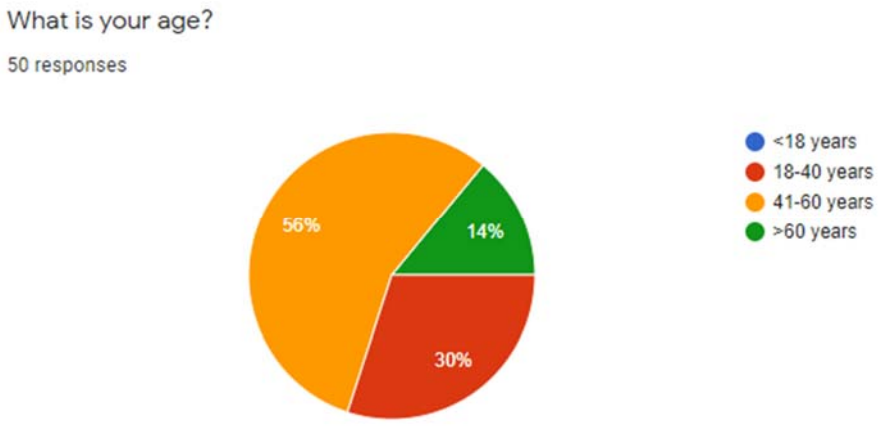
- 2 weeks ago
- 3 weeks ago
- 4weeks ago
- >4 weeks ago

4. Have you received both the shots?
    - Yes
    - No
5. Did you feel pain in the area of injection after vaccination?
    - Yes
    - No
6. Were there any other symptoms
    - Fever
    - Headache
    - Joint pain
    - Muscle pain
    - Nausea
    - Fatigue
    - No
7. Do you had any severe symptoms that forced you seek medical help?
    - Yes
    - No
8. Do you had any allergic reaction to vaccine?
    - Yes
    - No
9. Have you taken any pain killer after receiving the vaccine?
    - Yes
    - No
10. Have you faced any irregular periods or heavy bleeding during periods after vaccination?
    - Yes
    - No
11. Have you faced any of the following symptoms after vaccination?
    - Blurred vision
    - Fainting
    - Loss of control
    - Over movement in parts of the body
    - No
12. Have you felt pain in the abdomen or epigastric area after vaccination?
    - Yes
    - No
13. Have you felt pain in one or both legs?
    - Yes

- No

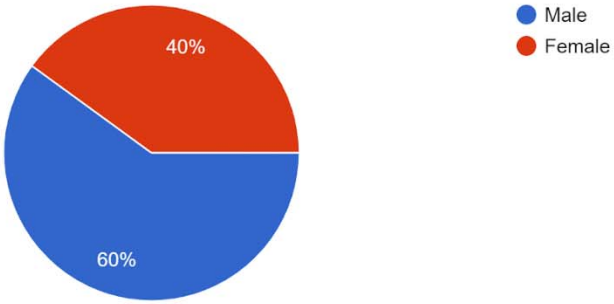
14. Have you noticed any swelling in the legs at the end of the day?
    - Yes
    - No
15. Do you had any sensation of sudden shortness of breath after receiving vaccine?
    - Yes
    - No
16. Do you have any chronic disease?
    - Diabetes
    - Hypertension
    - Both
    - No
17. Do you consume any habit forming substances?
    - Drinking
    - Smoking
    - Both
    - No

Annex 2 (Charts)



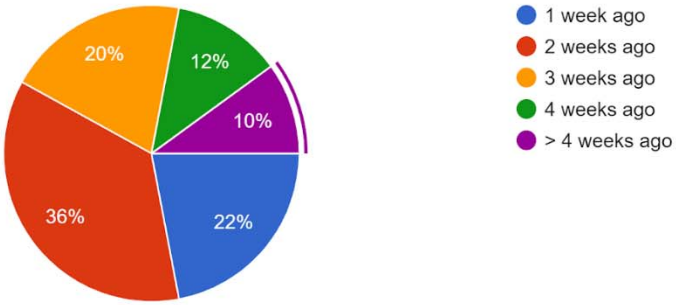
What is your gender?

50 responses



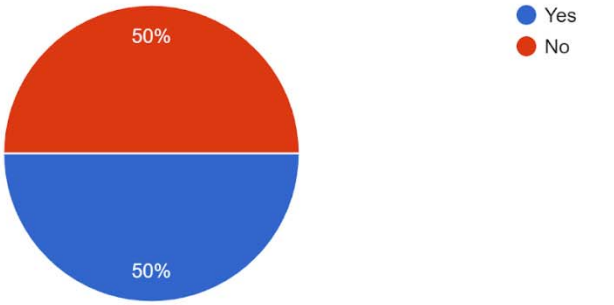
When did you receive your vaccine?

50 responses



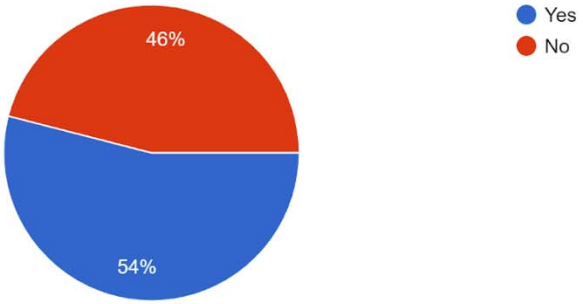
Have you received both the shots?

50 responses



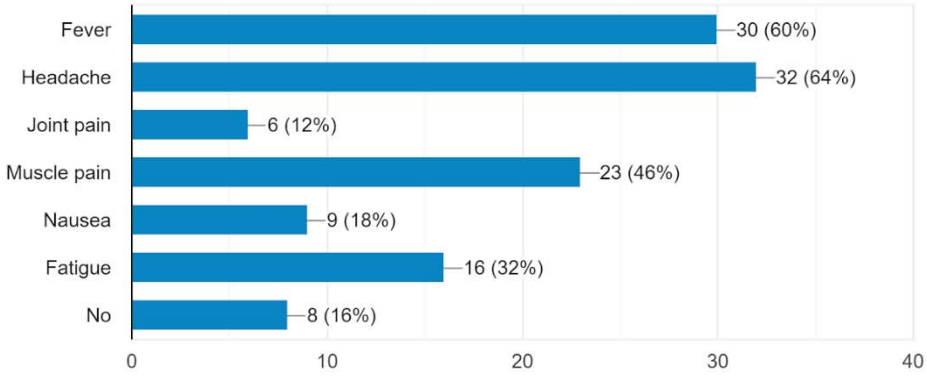
Did you feel pain in the area of injection after vaccination?

50 responses



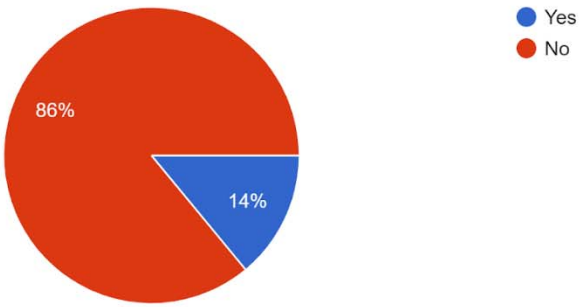
Were there any other symptoms?

50 responses



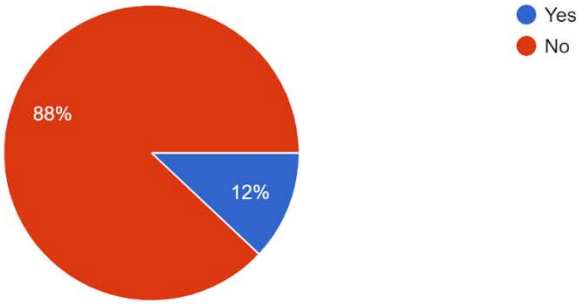
Do you had any severe symptoms that forced to you seek medical help?

50 responses



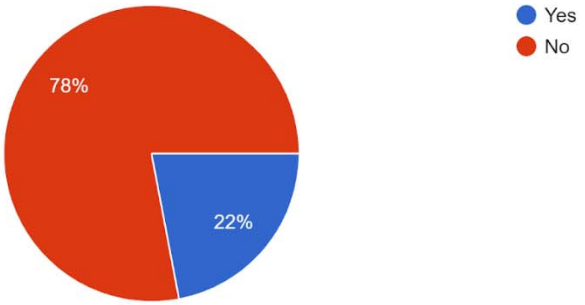
Do you had any allergic reaction to vaccine?

50 responses



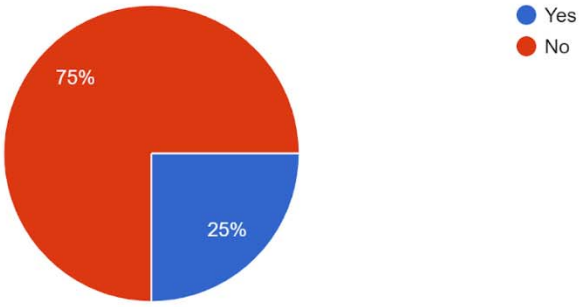
Have you taken any pain killer after receiving the vaccine?

50 responses



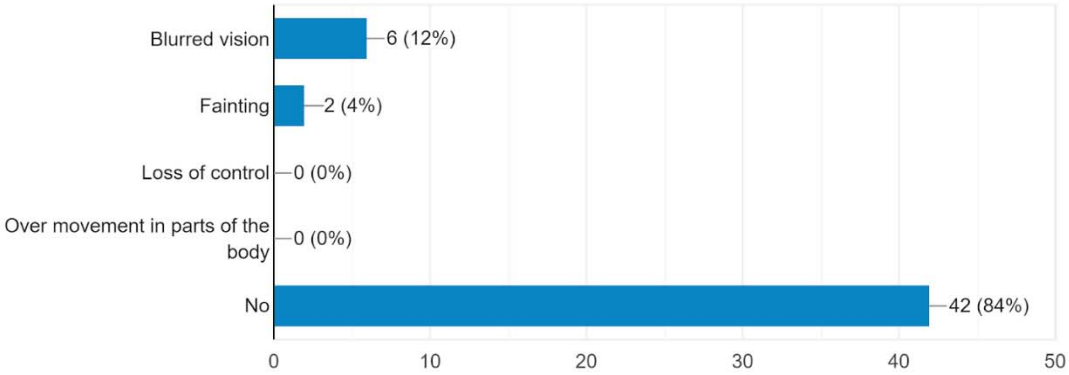
Have you faced any irregular periods or heavy bleeding during periods after vaccination?

20 responses



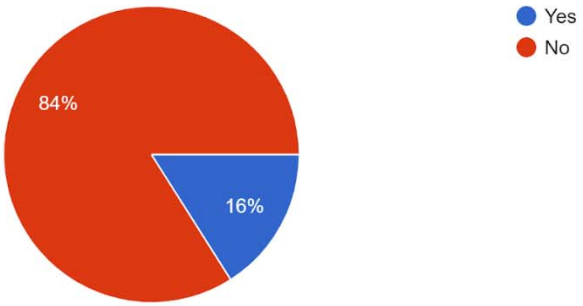
Have you faced any of the following symptoms after vaccination?

50 responses



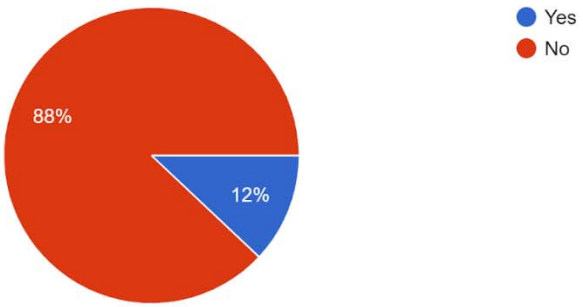
Have you felt pain in the abdomen or epigastric area after vaccination?

50 responses



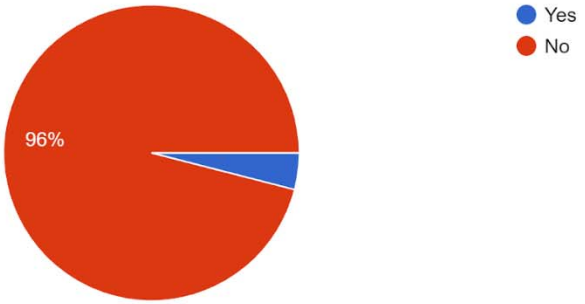
Have you felt pain in one or both legs after vaccination?

50 responses



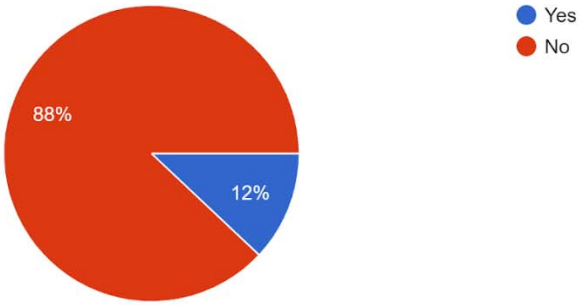
Have you noticed any swelling in the legs at the end of the day?

50 responses



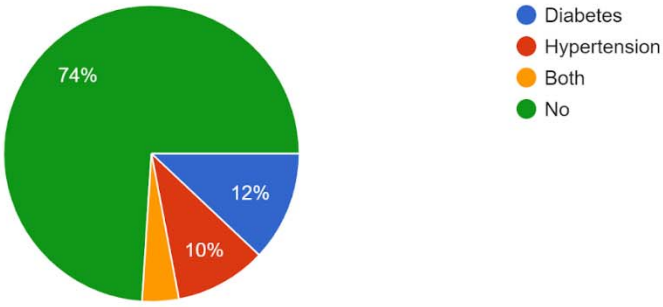
Do you had any sensation of sudden shortness of breath after receiving vaccine?

50 responses



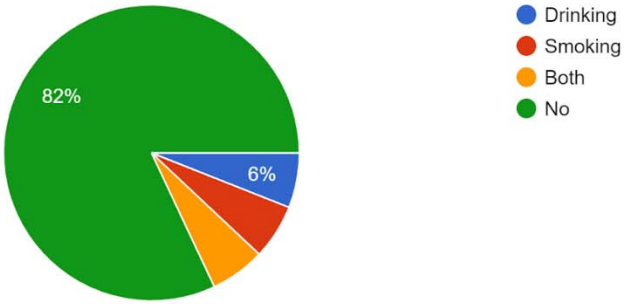
Do you have any chronic disease?

50 responses



Do you consume any habit forming substances?

50 responses



Prostate fusion biopsy results depending on prostate volume, PSA and PSA density analysis

Authors**:** Zane Zalužinska, University of Latvia, Faculty of Medicine, ‘’Treatment’’

Mentor: Egils Vjaters, Pauls Stradins Clinical University Hospital, Urology Center

Institutions involved in the study.

The study will be performed at the Urology Center of Pauls Stradins Clinical University Hospital, patients will be included in the study after confirmation of written consent. Subjects will be provided with standard medical care in accordance with the diagnosis and current treatment guidelines. No experimental or additional tests or investigative techniques will be performed in the study.

Aim

The aim of the study is to find out what factors influence the indications for imaging biopsy and what factors influence positive imaging biopsy in prostate cancer.

Tasks:

1. Collect clinical information, standard examinations, analysis and biopsy results.

2. To reveal influencing factors for indications for imaging biopsy and influencing factors for positive imaging biopsy in prostate cancer.

3. Data analysis and processing.

Planned number of research participants:

It is planned to involve ~ 150 research participants in the research

An Abstract

Prostate cancer (PC) is a widely recognized major medical problem worldwide. Global epidemiological trends in PC have been extensively studied. In terms of incidence, PC ranks fourth worldwide, with 1.1 million cases (7.9% of all cancers), and eighth in deaths, with 30,7000 cases (3.7% of all cancers). In 2012, PC was the second most common (15% of all newly diagnosed cancers) after lung cancer, and in terms of deaths, PC ranked fifth among men (6.6% of all cancers) after lung, liver, stomach and colorectal cancer. (Ferlay et al., 2015; Ferlay et al., 2013). Trends in cancer mortality over the last two decades have been declining in many regions - North America, Australia, New Zealand, Oceania, most of Northern and Western Europe (Center et al., 2012), associated with early diagnosis and better treatment (Collin et al., 20 08; Etzioni et al., 2008).

The diagnosis of prostate cancer is confirmed by histological examination of the biopsy material performed during transrectal ultrasonography. In a standard transrectal prostate biopsy, 8-12 tissue samples are taken from the entire prostate. Tissue samples are taken from different parts of the prostate to provide maximum information about different parts of the prostate. This is called

a systematic biopsy. The number of tissue samples depends on the size of the prostate. The biggest disadvantage of systematic biopsy is that the number and location of biopsies depends only on the biopsy performer - his skills and experience. According to the SPKC data, in 2017, 2145 prostate biopsies were performed in Latvia, in which 1286 new cases of prostate cancer were detected.

In 2008, Leite et al published a study in which 76 of 524 patients required a repeat prostate biopsy. Prostate cancer was detected in 10.5% of repeated biopsies. In addition, 25% of patients required more than 1 re-biopsy. In their 2009 study, Braun et al showed that 108 of 406 patients required a repeat biopsy and that 26.9% of repeat biopsies revealed prostate cancer.

A targeted prostate biopsy was introduced to reduce the number of repeat biopsies as well as to improve the accuracy of repeat biopsies. This method is based on the merging of pre-biopsy magnetic resonance imaging images with ultrasonography images during biopsy. During the procedure, it is possible to accurately locate the potential tumor site, resulting in a reduction in the number of biopsies and improved diagnostic accuracy of biopsies.

Find out what factors influence the indications for an imaging biopsy and what factors influence a positive imaging biopsy in prostate cancer.

Pathological test results such as elevated, free and total PSA levels, PSA density, prostate volume, PIRADS 4, Gleason> 6, Gleason upgrade, tumor localization and volume.

Keywords: Prostat cancer, fusion biopsy, PSA

Introduction

Materials and methods

A prospective study will be conducted, which will include patients who will be sent to Pauls Stradins Clinical University Hospital for an imaging biopsy due to suspicion of prostate cancer, and will be offered to participate in the study. The study will collect and analyze the results of a standard patient analysis and biopsy. No additional analyzes, examinations or questionnaires will be performed in the study. Patients who agreed to participate in the study and signed a consent form will collect data on patient age, prostate volume, prostate tumor volume on MRI, tumor profile on PRIRADS, PSA density, and tumor histology on biopsy material.

Informed consent

Patients will be provided with information about the course of the study, its purpose and significance, before starting the study. Study participants may opt out of the study after providing information. After the information about the study has been provided and all questions have been answered, you will be asked to sign a patient consent form, which will again provide information about the course and significance of the study.

The data will be anonymous and will not use the patient's personal information, but each patient will have an individual code (such as the letter combination a.b.). The data obtained will be stored in a statistical program that will be stored in the hospital.

At the end of the study, the data will be kept for at least five years.

Risks and benefits

No risks or benefits are expected for the patient to participate in the study.

Taking into account that no additional examinations will be performed during the patient's participation in the study, Pauls Stradins Clinical University Hospital is not expected to incur any additional expenses related to the implementation of the study.

The results of the study will help to improve the selection of patients for a targeted prostate biopsy in the future.

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