PMDC No. IP0042
ISSN (Online) 2309-592X ISSN (Print) 2309-3080
Volume 12, Issue 04, October-December 2016

Esculapio

Journal of Services Institute of Medical Sciences, Lahore.

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ESCULAPIO

JOURNAL OF SERVICES INSTITUTE OF MEDICAL SCIENCES, LAHORE.

VOLUME. 12 OCTOBER - DECEMBER 2016 ISSUE. 04

PUBLISHED BY

SERVICES INSTITUTE OF MEDICAL SCIENCES, LAHORE.

ONLINE EDITION

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Review Article

MEMORY AND ITS MECHANISM

Hamid Javaid Qureshi and Naila Hamid

Abstract : Memory; a higher intellectual function is ability to store experiences and information and to recall these voluntarily and involuntarily. Explicit or declarative memory is associated with consciousness. It is of two types; episodic (memory of events) and semantic (memory of words, rules and language. It involves hippocampus, amygdala and diencephalon. Implicit or skill or habits memory is the memory of skilled behavior and it does not require conscious understanding; for example riding a bicycle and playing basket ball. Parts of the brain involved in this memory are parts of sensorimotor cortex, basal nuclei and cerebellum.

Memory can be short term, intermediate long term and long term. Short term memory lasts for seconds to a few minutes. Short term memory is consolidated to long term memory by rehearsal or active practice. Minimum consolidation occurs in 5-10 minutes while strong consolidation requires 1 hour or more. Long term memory involves protein synthesis and permanent facilitation of synapses. Those sensory experiences are stored into memory that are accompanied by either reward or punishment.

Keywords: Explicit or declarative, implicit or skill memory, short term, long term, consolidation, reward, Punishment.

Introduction

Memory is one of the higher intellectual functions. It is ability to store experiences and information and to recall these consciously and unconsciously. The brain processes, stores and retrieves information in different ways to suit the need. The term memory encoding defines the neural processes that convert an experience into the memory.[1] It involves cellular or molecular changes specific to different memories.[2] Memory can be classified into two categories according to the type of information that is stored; declarative or explicit or precognitive memory and procedural or implicit or skill memory.[3]

Declarative or Explicit or Precognitive Memory:

It is associated with consciousness or at least awareness. It is memory of events (episodic memory) and memory of words, rules and language etc (semantic memory). It is the retention and recall of conscious experiences that can therefore be put into words (declared). One example is the memory of having perceived an object or event and, therefore, recognizing it as familiar and may be even knowing the specific time and place when the memory originated. Another example would be one's general knowledge of the world, such as names and facts.[3]

Procedural Or Skill Or Implicit Memory:

It is the memory for skilled behaviors and it does not require any conscious understanding, as for example, riding a bicycle. Individuals can suffer severe deficits in declarative memory but have intact procedural memory. One case study describes a pianist who learned a new piece to accompany a singer at a concert but had no recollection the following morning of having performed the composition. He could remember how to play the music but could not remember having done so. The category of procedural memory also includes learned emotional responses, such as fear of spiders, and the classic example of Pavlov's dog that learned to salivate at the sound of a bell after the bell had previously been associated with food. Implicit memory does not involve awareness, it includes skills, habits and conditioned reflexes. However explicit memory is initially required for activities such as riding a bicycle, it can become implicit once the task is thoroughly learned.[2] Our brain receives a lot of sensory information but the brain has capability to ignore information that is not useful. This capability results from inhibition of synaptic pathways through habituation and that is called negative memory. Useful information are stored as positive memory through facilitation of the synaptic pathways. The neural change responsible for retention or storage of knowledge is called-memory trace.[1] Some memories last for only a few seconds whereas others last for hours, months or years, so there is a common classification of memories that divides memories into three types; short term memory, intermediate long term memory and long term memory.[1,4]

Short Term Memory:

It registers and retains incoming information for a short time, a matter of seconds to minutes after its input. It is the memory that we use when we keep

information consciously in mind. For example a person looks a number in the telephone book and remembers it only long enough to walk across the room and dial it. Usually a telephone number of 7 to 10 digits can be retained for a short time. Short term memory is produced by continual neural activity resulting from nerve signals that travel around and around a temporary memory trace in a circuit of reverberating neurons. Other possible mechanisms are presynaptic facilitation or inhibition. This occurs at synapses that lie on terminal nerve fibrils immediately before these fibrils synapse with a subsequent neuron. The neurotransmitters secreted at such terminals cause facilitation or inhibition lasting for seconds upto several minutes.[1] During short term memory, the memory traces are subject to disruption by trauma and various drugs; whereas long term memory traces are remarkably resistant to disruption. Short term memory is also known as working memory. Working memory keeps incoming information available for a short time.[5]

There is a strong correlation between working memory and standard measures of intelligence. The specific memory deficit that occurs in early stages of Alzheimer's disease, a condition marked by dementia and serious memory loss, may be in this attention focusing component of working memory. The hormones released during stress such as epinephrine, glucocorticoids and vasopressin affect the retention of learned experiences. Coma, deep anesthesia, electroconvulsive shock and insufficient blood supply to the brain interfere with working memory.[2]

Intermediate Long Term Memory:

Intermediate long term memories may last for many minutes or even weeks. These are eventually lost unless the memory traces are activated enough to become more permanent. These memories result from temporary chemical or physical changes, or both, in either the presynaptic terminals or the postsynaptic membrane .These changes can persist for minutes upto several weeks.[1]

Long Term Memory:

It may last for years or even for the whole life such as knowledge of alphabets, basic facts and names of near relatives. The process of transferring and fixing short term memory traces into long term memory stores is known as consolidation **Fig-I** [6,7]. It is through active practice or rehearsal. Short term memory fades quickly unless consolidated into long term memory. Long term memory involves permanent functional or structural changes between existing neurons such as formation of new synapses, synthesis of new proteins. The process of consolidation requires 5-10 minutes for minimal consolidation and 1 hour or more for strong consolidation Rehearsal enhances the transfer of short term memory into long term memory. Long term memory results from actual structural changes at synapses instead of only chemical changes.[1] Long term potentiation is involved in the memory mechanism, in which certain synapses undergo a long lasting increase in their effectiveness when these are heavily used.[2] These structural changes will not occur if a drug is given that blocks DNA stimulation of protein replication in the presynaptic neuron and permanent memory trace will not develop. The most important physical structural changes are.[1]

1- Increase in number of transmitter vesicles released.
2- Increase in vesicle release sites for secretion of transmitter substance
3- Increase in number of presynaptic terminals.
4- Changes in structures of the dendritic spines that permit transmission of stronger signals.

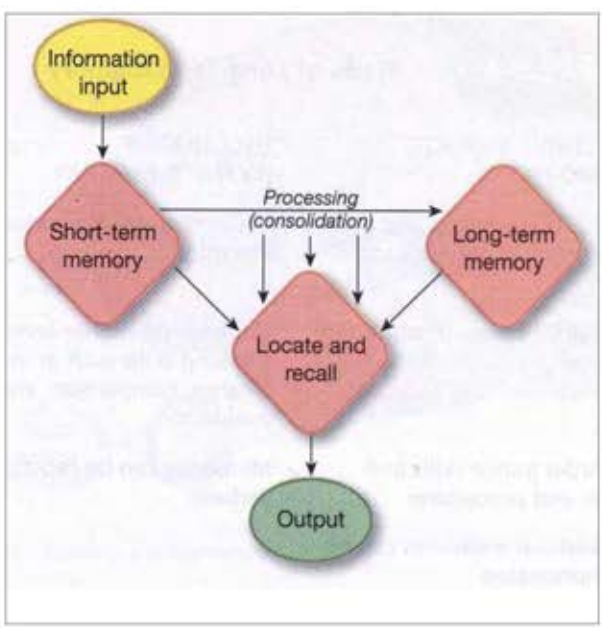

Fig-1: Consolidation of short term memory into long term memory.[7]

Long-term memories are believed to consist of some kind of structural changescalled engramsin the cerebral cortex. Widely accepted today is the theory that an engram consists of some kind of permanent change in the synapses in a specific circuit of neurons. It may represent an increase in the number of presynaptic axon terminals or an increase in the

number of receptor proteins in the postsynaptic neuron's membrane. Changes in second messenger systems and protein synthesis occur during long term memory.[2] There may be changes in the average concentration of neurotransmitters at certain synapses or changes in the functions of astrocytes. Whatever the changes are, these somehow facilitate impulse transmission at the synapses. The storage capacity of the long term memory bank is more extensive than the capacity of short term memory. Visual memories are stored separately from anditory memories. Some long term memories (information or skills) of daily use are never forgotten such as names of near relatives or alphabets. Remembering is the process of retrieving specific information from memory stores. Forgetting is the inability to retrieve stored information.[6]

Retrograde (going backward) amnesia is the inability to recall recent past events. It usually follows concussion or stroke. Anterograde (going forward) amnesia is inability to store memory on long term basis. It is associated with lesion of medial temporal lobe, these patients cannot establish new permanent memories. They can recall things they learned before the onset of their problems.[6]

Parts of the brain involved:

There is no single "memory center" in the brain. Neurons involved in memory traces are widely distributed in the cortical and subcortical regions of the brain.[5] The regions of brain most extensively involved in memory include the hippocampus, medial temporal lobes, limbic system, cerebellum and prefrontal cortex.[6,8] The temporal lobes appear to be particularly important for memory because bilateral removal of the hippocampus severely and permanently disrupts recent memory. Short-term and long-term memories are unaffected, but new long-term memories can no longer be stored. Thus, patients with such deficits remember events before their surgery but fail to recall new events, even with multiple exposure, and must be reintroduced to their therapists repeatedly. This is a loss of declarative memory involving the conscious recall of personal events, words and their meanings, and general history. Such patients, however, can still learn some tasks because they retain procedural memory, the ability to acquire problem-solving, association, and motor skills. If patients are given a complex task to perform (e.g., mirror writing), they will not only improve during the first training session but will also perform better on subsequent days despite their denial of having any experience with the task.[5] The hippocampus, amygdala and diencephalon play an important role in short term memory and declarative memory. The cerebellum, basal ganglia and regions of sensorimotor cortex play an essential role in procedural memories involving motor skills gained through repetitive training. The prefrontal cortex is involved in the complex reasoning skill associated with working memory Working memory areas are connected to the hippocampus and adjacent parahippocampal portions of the medial temporal cortex **Fig- II.**[2]

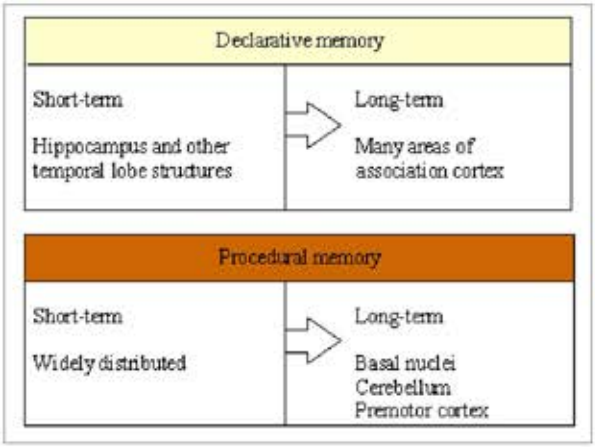

Fig-2: Brain areas involved in encoding and storage of declarative and procedural memories.[2]

The key to memory is alteration in the strength of selected synaptic connections which involves protein synthesis and activation of genes. This occurs during the change from short term memory to long term memory. Long term memory leads to activation of genes that produces increases in synaptic contacts. In humans, bilateral destruction of the ventral hippocampus, or Alzheimer's disease and similar disease process that destroys its neurons cause marked defects in short term memory. Human with such destruction have intact working memory and remote memory. Their implicit memory processes are generally intact. The connections of the hippocampus to especially mamilliary bodies and anterior thalamic nuclei are also involved in memory. Long term memories are stored in various parts of the neocortex. Once long term memories have been established, these can be recalled or accessed by a large number of different associations. For example, the memory of a vivid scene can be evoked by a sound or smell associated with the scene.[5]

Many research findings indicate that the cerebrum's limbic systemthe "emotional brain"plays a key role in memory.

To mention one role, when the hippocampus (part of the limbic system) is removed, the patient loses the ability to recall new information. Personal experience substantiates a relationship between emotion and memory.[7] Sensory experiences that are not accompanied by reward or punishment are hardly remembered. An animal builds up strong memory traces for sensation that are either rewarding or punishing.[1] The absolute amount of REM sleep has been correlated with intellectual functioning in the elderly.[9] REM sleep levels are shown to be diminished in Alzheimer's patients.[10]

Hormal control of memory:

Certain hormones like adrenocorticotrophic hormone (ACTH), epinephrine and vasopressin released during stressful or even mild stimulating condition, affect memory. Enkephalin and endorphin interfere with learning and memory during painful experiences because these decrease emotional (fear, anxiety) components of the painful experience associated with learning, there by reducing the motivation necessary for learning.[11]

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Original Article

Effect of Serum Albumin on Outcome of Stroke In Children at Tertiary Care Hospital

Muhammad Usman Khalid, Muhammad Shahid, Faiqa Saleem Baig and Tipu Sultan

Objective: The objectives of this study were to determine the frequency of favorable outcome of stroke in children presenting at tertiary care hospital and to compare the mean serum albumin levels in children with favorable and unfavorable outcome of stroke in tertiary care hospital.

Methods: Two hundred children in the age range of 1-14 years, meeting the inclusion and exclusion criteria were registered from pediatric and neurology department of Children Hospital & ICH Lahore. Informed consent was taken from their parents to include them in the study. Demographic information (name, age, sex, address) was collected. Serum albumin was sent to biochemistry lab of the hospital at the time of admission. Outcome of the stroke was determined by Modified Rankin Scale at the time of discharge and death in case and observed data was recorded on a specially designed proforma (attached).

Results: In our study, out of 200 cases, 40% (n=80) cases were between 1-7 years of age, 60% (n=120) cases were between 8-14 years of age, mean±sd was calculated as 7.75±3.49 years, 56% (n=112) cases were male, 44% (n=88) cases were females. Frequency of favorable outcome of stroke in children with stroke presenting in tertiary care hospital was calculated as 42.5% (n=85) while 57.5% (n=115) had unfavorable outcome. Comparison of mean serum albumin levels in children with favorable and unfavorable outcome of stroke in tertiary care hospital showed, 3.13±0.19g/dl in favorable outcome while 1.79±0.18g/dl in unfavorable outcome and p value was calculated as 0.0001 which shows a significant difference between mean serum albumin levels in favorable and unfavorable outcome of stroke.

Conclusion: We concluded that most of the pediatric stroke patients have unfavorable outcome and comparatively less patients have favorable outcome of stroke. Also, the mean serum albumin level in children with favorable outcome is higher and it is significantly lower in children with unfavorable outcome of stroke in tertiary care hospital. So higher the serum albumin in pediatric stroke patient one can expect good outcome of stroke.

Keywords: Stroke in children, favorable outcome, mean serum albumin levels.

Introduction

An acute onset of focal neurological deficit persisting more than 24 hours is called stroke. Some pediatric neurologists include more transient deficit.[1] In neonates, about one of every 4,000 live births suffer from stroke and the risk of stroke from birth through age 18 is nearly 11 per 100,000 children per year.[2] Also, the top 10 causes of death for children includes stroke.[3] Two Asian studies reported incidences of pediatric stroke on population basis, first in Hong Kong and second study in an Iranian province, estimated an incidence of 2.1 per 100,000 children per year and an incidence of 1.8 per 100,000 children per year, respectively. Stroke resulting from vascular occlusion is ischemic stroke and from vascular rupture is haemorrhagic stroke .[4] Childhood stroke include death in 6-10%, seizure disorders in 15% and neurological deficit in 60-70% of patients.[5]

Albumin is produced in liver and it is the most abundant blood plasma protein constituting about 50% of human plasma proteins. It is a multifunctional protein. It maintains the oncotic pressure of the blood compartment which regulates blood volume. It also help in carrying the molecule including lipid soluble hormones, bile salts, unconjugated bilirubin, free fatty acids, calcium, transferrin, and some drugs.[6] This protein has been implicated in many neurological diseases because of its anti-oxidant property. Its ability to regulate the brain circulation and to modulate intracellular signalling of neuronal or glial cells are attributed as its direct neuroprotective actions.[7]

It has been found in various studies that the serum albumin is useful in predicting the functional outcome in stroke patients.[8,9] A study including 75 stroke patients determined mean serum albumin level in patients with good outcome of stroke and poor

outcome of stroke was 3.03± 0.61 and 2.08±0.61, respectively .[10] Patients that died had significantly lower serum albumin (1.66g/dl) than survivors (p=0.0001). Favourable outcome of stroke was reported in 48% of patients while 30-day case fatality was in 17.3% of patients. In experimental models, administration of albumin to rats have proven the increased neuroprotection in both ischemicand hemorrhagic stroke.[11]The rationale of study is to compare the mean serum albumin levels in children with favorable and unfavorable outcome of stroke. To the best of our knowledge, the effect of serum albumin on stroke outcome in pediatric population is not known. All studies have been carried out in adult population. This will help us to determine the prognosis of stroke early in the course of disease in children and proper rehabilitation programs may be provided in time, limiting the morbidity and the cost of management.

Methods

The study performed was descriptive case series study carried out at pediatric medicine and neurology department of The Children's Hospital and The Institute of Child Health, Lahore. Two hundred patients meeting inclusion and exclusion criteria, were enrolled in the study from 13 June to 13 December after taking informed consent from parents. Sampling technique was non purposive probability sampling. The inclusion criteria involved every patient with any acute neurological deficit persisting for more than 24 hours, confirmed on CT scan having age from 1 year to 14 years and patients with hemorrhagic or ischemic stroke. The exclusion criteria involved patients with transient neurological deficit less than 24 hours, head injury, any organic brain pathology and recurrent attack of stroke.

Serum albumin was sent to biochemistry lab of the hospital at the time of admission. Outcome of the stroke was determined by Modified Rankin Scale at the time of discharge and death in case. All data was collected into predesigned proforma(attached).

Data obtained were analysed using SPSS 17.0. All quantitative data like age and mean serum albumin levels were presented by mean and standard deviation. All qualitative data like gender and favorable outcome (i.e. score 0-3) was presented in the form of frequencies and percentages. Student t-test was used to compare the mean serum albumin levels in both groups (i.e. favorable and unfavorable). A p value ≤0.05 was considered as significant.

Results

A total of 200 cases fulfilling the inclusion/exclusion criteria were enrolled to determine the frequency of favorable outcome of stroke in children with stroke presenting in a tertiary care hospital and to compare the mean serum albumin levels in children with favorable and unfavorable outcome of stroke in tertiary care hospital. Age distribution of the patients was done which shows that 40% (n=80) cases were between 1-7 years of age, 60% (n=120) cases were between 8-14 years of age, mean+sd was calculated as 7.75±3.49 years.**(Table No. 1)**

Table-1: Age distribution (n=200).

Age (in years)	No. Of Patients	Percentage
1-7	80	40%
8-14	120	60%
Total	200	100%
Mean±SD	7.75±3.49	

Table-2: Gender distribution (n=200).

Age (in years)	No. Of Patients	Percentage
Male	112	56%
Female	88	44%
Total	200	100%

Table-3: Mean serum albumin levels in children with stroke in tertiary care hospital (n=200).

Serum albumin	Mean	SD
	2.36	0,69

Table-4: Frequency of favorable outcome of stroke in children with stroke presenting in tertiary care hospital (n=200).

Favourable Outcome	No. Of Patients	Percentage
Yes	85	42.5%
No	115	57.5%
Total	200	100%

Table-5: Comparison of mean serum albumin levels in children with favorable and unfavorable outcome of stroke in tertiary care hospital (n=200)

Serum albumin levels			
Favourable outcome		Unfavourable outcome	
Mean	SD	Mean	SD
3.13	0.19	1.79	0.18

P value=0.0001

Gender distribution of the patients was done which shows that 56% (n=112) cases were male, 44% (n=88) cases were females.**(Table No. 2)**

Mean serum albumin levels in children with stroke in tertiary care hospital were calculated as 2.36±0.69 g/dl. **(Table No. 3)**

Frequency of favorable outcome of stroke in children with stroke presenting in tertiary care hospital was calculated as 42.5% (n=85) while 57.5% (n=115) had unfavourable outcome. **(Table No. 4)**

Comparison of mean serum albumin levels in children with favorable and unfavorable outcome of stroke in tertiary care hospital shows 3.13±0.19 g/dl in favourable outcome while 1.79±0.18 g/dl, p value was calculated as 0.0001 which shows a significant difference between favourable and unfavourable outcome. **(Table No. 5)**

Discussion

Stroke is rare in pediatric age group but it has significant morbidity and mortality burden. To optimize the outcome of stroke in children it is required to understand that children with stroke present differently than adults and many of them present with unique risk factors. We know the neuroprotective role of albumin with all its pivotal role in hemodynamics of human body also serum albumin level is one of the biochemical markers of nutritional status, and malnutrition after acute stroke is a risk factor for poor outcome.

We planned this study to compare the mean serum albumin levels in children with favorable and unfavorable outcome of stroke as, the effect of serum albumin on stroke outcome in pediatric population is not known while all studies have been carried out in adult population.

In our study, out of 200 cases, 40% (n=80) cases were between 1-7 years of age, 60% (n=120) cases were between 8-14 years of age, mean±sd was calculated as 7.75±3.49 years, 56% (n=112) cases were male, 44% (n=88) cases were females. Frequency of favorable outcome of stroke in children with stroke presenting in tertiary care hospital was calculated as 42.5% (n=85) while 57.5% (n=115) had unfavourable outcome. We also compared of mean serum albumin levels in children with favorable and unfavorable outcome of stroke in tertiary care hospital shows 3.13±0.19 g/dl in favourable outcome while 1.79±0.18 g/dl, p value was calculated as 0.0001 which shows a significant difference between mean serum albumin level of children with favourable and unfavourable outcome of stroke.

We correlated our study with a prospective study including 75 stroke patients which determined mean serum albumin level in patients with good outcome of stroke and poor outcome of stroke was 3.03± 0.61 and 2.08±0.61, respectively .[10]Favourable outcome of stroke was reported in 48% of patients while 30-day case fatality was in 17.3% of patients.

A few studies suggest that increased risk of stroke is associated with low serum albumin level. In one prospective study group with high serum albumin (>44 g/l) vs. low serum albumin (<42 g/l) had reduced stroke incidence. In the cross-sectional Norwegian Oslo Health Study, low albumin (less than or equal to47 g/l) was associated with increased prevalence of self-reported stroke (OR: 1.83; 95% CI: 1.202.78) after adjusting for age and sex.[14]

We did not find much data to compare our results as no such study is available in children, however, our findings in our local population are primary, while some other trials are required so that our results may be authenticated and proper rehabilitation programs may be provided in time, limiting the morbidity and the cost of management as well. Also experimental models in children may be started regarding institution of albumin therapy in stroke patients so as to decrease the morbidity.

Conclusion

We concluded relatively lower frequency of favorable outcome of stroke in children and higher mean serum albumin level in children with favorable outcome while significantly lower mean serum albumin level in children with unfavorable outcome of stroke in tertiary care hospital.

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Picture Quiz

What can you interpret from following chest x-ray ?

See Answer on page# 207

Original Article

Serum Zinc and Immunoglobulin G Levels in Lower and Upper / Upper Middle Socioeconomic Groups

Uzair Mumtaz, Hamid Javaid Qureshi and Muhammad Usman Bashir

Objective: To assess the serum zinc and serum immunoglobulin G levels in different socioeconomic groups.

Methods: Hundred subjects in total were investigated. Out of these, 50 (25 males and 25 females) belonged to the lower socioeconomic (LSEC) group and 50 (25 males and 25 females) belonged to the upper / upper middle socioeconomic (USEC) group. Estimation of serum zinc was made by colorimetric method whereas serum immunoglobulin G (IgG) was determined by the immunoturbidimetric assay. A comparison of both parameters was made between the two socioeconomic (SEC) groups.

Results: Results revealed significantly low serum zinc in the LSEC group as compared to the USEC group. Similarly serum IgG levels were also significantly low in the LSEC group. Serum IgG levels did not show significant gender difference in the LSEC group however it was significantly higher in females than in males in the USEC. Generally a significantly positive correlation was found between serum zinc and serum IgG levels.

Conclusion: The LSEC class has low serum zinc levels and low serum IgG levels and hence is at greater risk of developing infections.

Keywords: Zinc, immunoglobulin G, socioeconomic status.

Introduction

Trace elements or trace minerals are proven to be essential for optimal growth and development of human body.[1] Zinc is an essential trace element for all forms of life and is necessary for optimal growth and development of human body.[2] It exists in nearly every cell of the body.[3,4] It is the second most abundant metal in organisms (second only to iron). Human body contains about 2-3 g of zinc. Of this, 60% is present in skeletal muscle and 30% in bone. Remaining is present in body fluids.[5,6]

Zinc plays a significant role to provide immunity to the body. It is crucial not only for the normal development and functions of cells mediating non specific immunity but also for the development of acquired immunity, like the immunoglobulin production.[7] Fortes et al (1998) reported that zinc supplementation improves cell mediated immune response in older population.[8] Zinc supplementation potentiates the effects of antiseptic agents.[9] Zinc is an excellent antioxidant. It gets rid of free radicals that cause damage to cells in the body by bonding with them and neutralizing them.[10] Neutrophil chemotaxis is impaired in zinc deficiency.[11] Compared with residents who had low zinc levels, people with normal levels had fewer cases of pneumonia, required fewer antibiotic prescriptions for it, and when they did get pneumonia, they had it for fewer days. Zinc supplementation also resulted in stronger humoral responses against antigenic challenges particularly in raising immunoglobulin G and immunoglobulin M levels in sheep.[12] In zinc deficiency, not only is the total amount of antibodies diminished; even the repertoire of antigens recognized by these antibodies is depressed. Interestingly this effect is even seen in mild or transient zinc deficiency during pregnancy.[7] Certain developmental steps responsible for B-cell receptor repertoire maturation thus seem to be dependent on zinc.[13]

The richest sources of zinc are meat, milk products, shell fish (oyster) and poultry while fruits and vegetables are poor sources.[14,15] Oyster contains the largest content of zinc which is 188.5 341 mg / kg. Human breast milk has higher concentration of zinc.[16] When given orally, zinc is absorbed from the small intestine.[17] Zinc is excreted through feces, urine and sweat.[18] A number of factors affect the absorption of zinc.[2] It is widely accepted that of the numerous dietary factors known or suspected to affect zinc absorption, zinc and phytate content have the greatest effect.[19] Phytates which are present in foods like cereals, corn, rice and vegetables have a strong negative effect on zinc absorption from composite meals. Inositol hexaphosphates and pentaphosphates are the phytate forms that exert

these negative effects on zinc absorption.[20] Zinc deficiency is associated with diets based on plant foods which are rich in zinc absorption inhibitors. Such diets are habitually consumed in rural areas and in economically poor areas of the cities.[21]

The above facts reveal that Zinc deficiency may occur in those individuals who do not take animal foods. Majority of poor people in Pakistan do not afford animal foods due to their high prices and hence consume foods of vegetable origin. Food of vegetable origin contains phytates which are zinc absorption inhibitors. Hence the poor population of Pakistan is likely to be suffering from zinc deficiency and immunodeficiency. The present study was planned to assess zinc levels and serum IgG levels in LSEC and USEC groups.

Methods

It was a cross sectional analytical study. It was conducted in the Department of Physiology, Services Institute of Medical Sciences, Lahore on a total of 100 healthy subjects. Their ages were between 10 to 30 years. Fifty subjects (25 males and 25 females) belonged to the LSEC group and 50 (25 males and 25 females) belonged to the USEC group. The subjects having average monthly income of less than 3200 rupees per capita per month (US$ 0-1.25 per capita per day) were included in the LSEC group. The subjects having a family income of more than 4000 rupees per capita per month and living in their own house were included in the USEC group.[22] Informed consent of the subjects was obtained. History taking and general physical examination of the subjects were carried out. Individuals who were diabetic, hypertensive, smokers and those taking any medication or drugs especially steroids, vitamin supplementation or minerals were excluded on history. Five milliliters (ml) of blood was drawn aseptically from each subject. The blood was centrifuged at 2500 rpm for 10 minutes at room temperature. Serum was separated and stored at 4°C. Serum zinc was determined by colorimetric method using the kit manufactured by Spectum.[23] Serum IgG was estimated by immunoturbidimetric assay[24] using Roche kit. Roche IgG assay is based on the principle of immunological agglutination. Data analysis was carried out with the SPSS version 19 (SPSS, Inc, Chicago, IL, USA). Arithmetic mean and standard deviation (SD) of each parameter were determined. The significance of differences among the groups was analyzed by student's t-test. Pearson's correlation was used to determine correlation between serum zinc and neutrophil percentage phagocytosis. A p-value < 0.05 was considered statistically significant.

Results

(Table-1) shows a comparison of serum zinc and Serum lgG between the two socioeconomic groups. Serum zinc was significantly higher (p=0.000) in the USEC group as compared to the LSEC group. Similarly, the serum lgG was significantly higher (p=0.000) in the USEC group as compared to the LSEC group. **(table-2)** depicts that serum zinc was significantly higher in the male subjects (p=0.000) in the USEC group as compared to males in the LSEC group. Similarly, in the female subjects, serum zinc was significantly higher (p = 0.000) in the USEC group as compared to the LSEC group. Same is the case with the serum lgG, which was significantly higher in USEC group as compared to LSEC group in both males (p=0.004) and females (p=0.000). Gender difference of parameters within USEC group as shown in **(table-3)** reveals that serum zinc difference was not significant (p=0.089). Serum lgG in males was significantly less (p=0.000) than in females. Both serum zinc and serum lgG did not show any significant gender difference in the LSEC group **(table-4)**. There was a significant positive correlation of serum lgG with serum zinc in total subjects of USEC group (r=0.323, p= .022) and the male subjects of LSEC group (r=0.469, p=0.018) but no significant correlation was found in total subjects of LSEC group and in male subjects of USEC group **(table-5, fig-1, 2)**.

Table-1: Comparison of serum zinc and Serum lgG in total subjects in the two socioeconomic groups.

Parameter	USEC Group (n=50)	LSEC Group (n=50)	P-value
Serum Zinc (ug/dl)	111.05±13.66	77.28±14.90	0.000*
Serum 1gG(mg/dl)	1430.82±276.26	1065.44±328.93	0.000*

Table-2: Comparison of serum zinc and Serum lgG in male and female subjects in the two socioeconomic groups.

Paramters	Males		P-value	Females		P-value
	USEC group (n=25)	LSEC group (n=25)		USEC group (n=25.)	LSEC group (n=25)	
Serum zinc (ug/dl)	107.76±14.29	76.72±8.56	0.000*	114.33±12.42	77.83±19.48	10.000*
Serum1gG (ud/dl)	1288.16±268.33	1044.48±307.19	0.004*	1573.48±203.53	1086.40±354.42	0.000*

Table-3: Gender difference of parameters within upper/ upper middle socioeconomic group.

Parameter	Males (n=50)	Females (n=50)	P-value
Serum Zinc (ug/dl)	107.76±14.29	114.33±12.42	0.0089
Serum 1gG(mg/dl)	1288.16±268.33	1573.48±203.53	0.000*

Table-4: Gender difference of parameters within Lower socioeconomic group.

Parameter	Males (n=50)	Females (n=50)	P-value
Serum Zinc (ug/dl)	76.72±8.56	77.83±19.48	0.796
Serum 1gG(mg/dl)	1044.48±307.19	1086.40±354.42	0.657

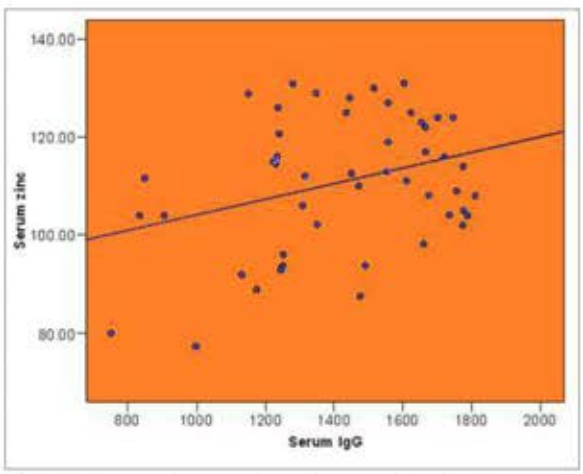

Fig-1: Scatter diagram showing positive significant correlation (n=50, r=0.323, p=0.022) between serum zinc and serum IgG in total subjects of USEC group.

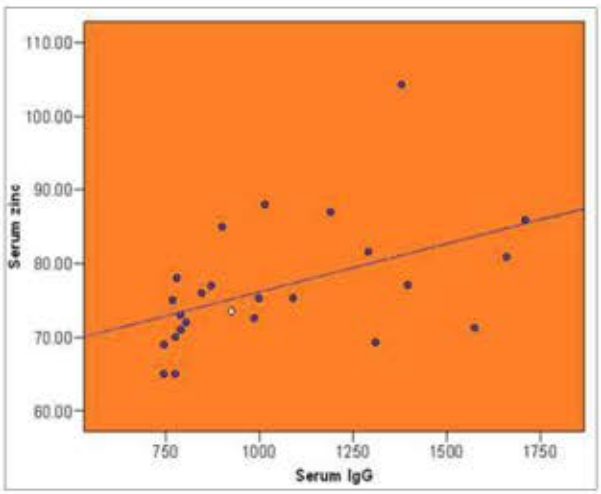

Fig-2: Scatter diagram showing positive significant correlation (n=25, r=0.469, p=0.018) between serum zinc and serum IgG in males of LSEC group

Table-5: Correlation of serum zinc with Serum IgG in the two socio economic groups. Correlation coefficient (r) and p.value are given.

Correlation of serum Zinc with	USEC (n=50)		LSEC (n=50)	
	r Value	p value	r value	p-value
Serum1gG (ud/dl)	0.323	0.022*	-0.099	0.493

** p <0.05 — Significant*

Table-6: Correlation of serum zinc with serum IgG in male and female subjects in the two socioeconomic groups. Correlation coefficient (r) and p.value are given.

Correlation of serum zinc with	USEC Group				LSEC Group			
	Male (n=25)		Female (n=25)		Male (n=25.)		Female (n=25)	
	r value	p value	r value	p value	r value	p value	r value	p value
Serum1gG (ud/dl)	0.212	0.309	0.277	0.181	0.469	0.018*	-0.326	0.112

** p <0.05 — Significant*

Discussion

The present study was conducted on 100 healthy subjects of LSEC class and USEC class. Serum zinc levels were found to be significantly low in the LSEC as compared to the USEC group in the total number of subjects as well as in the male and female subgroups. The deficiency of zinc is associated with diets based on plant origin, which are rich in zinc absorption inhibitors like phytates. All cereals and vegetables contain phytates which can bind zinc and reduce its biological availability.[19] Phytates are co-precipitated with zinc and absorption of zinc is decreased.[25] The LSEC class of our country being unable to consume animal diet due to its high price and mostly take vegetable diet, so is at the risk of low serum zinc levels.

Zinc is necessary for the normal function of the immune system. Even mild zinc deficiency, which is widely spread in contrast to severe zinc deficiency, depresses immunity of humans. B cells represent the main cells of humoral immunity. After stimulation, B cells differentiate to antibody producing plasma cells. B lymphocytes and their precursors (especially pre-B and immature B cells) are reduced in absolute number during zinc deficiency, Thus, there are fewer naive B cells during zinc deficiency that can react on neoantigens. Taking into account that the number of T cells is also reduced during zinc deficiency and that the most antigens are T-cell dependent, it is probable that with zinc deficiency, the body is unable to respond with antibody production in response to neoantigens. This assumption is consistent with

findings that show that B-lymphocyte antibody production is disturbed during zinc depletion.[26] In the current study it was found that serum IgG was significantly higher ($p < 0.01$) in the USEC group as compared to the LSEC group. It was significantly low in the male LSEC ($p < 0.01$) group as well as in the female LSEC group ($p < 0.01$). There was a significant positive correlation between serum zinc and serum IgG levels in the present study. Also in this study it was found that serum IgG was significantly more in females as compared to males in the USEC group but no such finding was observed in the LSEC group

Conclusion

Serum zinc level is significantly low in the lower socioeconomic class. A significant positive correlation is found between serum zinc and serum IgG levels.

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Original Article

Paucity of Nosocomial Surveillance Programmes, Infection Prevention and Control Practices in Pakistan: Impact of International Nosocomial Infection Control Consortium in the Developing Countries (INICC)

Faria Malik, Tariq Zulfiqar, Mubashir Razaque and Hanaa Noor Malik

Objective: To isolate/identify device associated bacteria with their antibiotic sensitivity/resistance patterns in 2015 and to compare them with such 2010 results. Further the impact of MSDS on device associated infections.

Methods: This cross-sectional study was carried out by the Microbiology Laboratory on devices or device-associated samples from intensive care units of Services Hospital Lahore in 2015. Bacteria were identified and their antibiotic sensitivities/resistance were tested.

Results: Samples submitted by ICUs were 446 with 302 from devices. Tracheal samples were 189(62.6%) whereas CV tips (30%)and Folleys catheter (4.3%). Growth positive samples were 219 (72%). Non fermentors comprised 54 % isolates with Acinetobacter predominating (33%) followed by Pseudomonas(21.8%). Enterobacteriaceae were 44% with E coli(16%) Klebsiella (12%) Proteus (10.7%) and Citrobacter (5.9%). Gram positive isolates comprised (n=23) isolates. Oxacillin resistant were (n=4). Acinetobacters (n=20) Pseudomonas (n=15) and Enterobactericeae (n=18)with Klebsiella (n=12) were resistant to all drugs tested. ESBLs were 14.

Conclusion: DAIs are a serious threat in ICU. Surveillance Programmes should be carried out under guidance of INICC.

Keywords: ICU, devices, acinetobacter, pseudomonas, enterobacteriaceae.

Introduction

Globally Surveillance Programmes for nosocomial infections have a positive impact[1,2,3] both in terms of reduction in infection,[4] morbidity, mortality and economy.[5,6] Intensive care units are a nidus of such infections[7] due to immuno-compromised population segregation[8] and use of devices.[9] Pakistan is a developing country with a poor population. There is a paucity of participation in such international infection control programmes but the Punjab Health Commission in 2014 implemented the Minimum Service Delivery Standards [MSDS][10] The samples submitted before and after the implementation of PHC will reflect of any change in Device Associate Infections(DAIs) in ICUs of a tertiary care hospital.

Methods

These cross-sectional, observational studies were carried out at the Microbiology Section, Department of Pathology, and Services Institute of Medical Sciences from the periods January to December 2010 & January to December 2015 on intensive care units of Services Hospital Lahore. Clinical specimens from devices were obtained from Medical & allied and Surgical & allied ICUs. These included tracheal aspirates, tips from unidentified source, urine catheter tips, central venous tips and drainage tubes. These samples were transported to the laboratory within 2 hours of collection.

Samples were cultured onto appropriate culture media as Blood agar, MacConkey's agar, Chocolate agar and CLED medium. Culture plates were incubated aerobically for 24-48 hours at 37C^0. Isolates were identified by colony morphology, Gram's staining, catalase, coagulase, oxidase and relevant biochemical tests.[11]

Antimicrobial sensitivity testing was performed on Mueller Hinton agar using Kirby-Bauer Disc Diffusion Method12.Antibiotic discs used for Gram negative bacteria were Ampicillin, Augmentin, sulfamethoxazole/trimethoprim, Ceftrioxone, Cefoperazone, Doxycycline, Azectam, Ofloxacin, Imipenem, Amikin, Tazobactam and Tigycycline. Antibiotic discs used for Gram positive isolates were Ampicillin, Augmentin, Vancomycin, Oxacillin, Ciproxin, Erythrocin, Doxycycline, Gentacin. Septran, Linezolid and Fucidic acid. All the antibiotic discs used in the present study were manufactured by Oxoid UK.

In the present study, DAIs, their associated bacteria,
and their sensitivity/resistance to antibiotics were studied. Organisms resistant to major / all the above groups of antibiotics were labelled as Resistant (R) organisms either MDR or Pan resistant. The results were analyzed and reported.

Results

In 2010, a total of 886 samples were submitted for culture and sensitivity from Services Hospital Lahore to the Microbiology Section of Services Institute of Medical Sciences Lahore. Devices or device-associated samples comprised almost 40% (n=350) of these samples. Growth was yielded by 267(76%) samples whereas 83 samples were growth negative. Tracheal samples were 60% followed by CV tips 27%. Folley's catheter samples were 12%. **(Table 1)**

Positive cultures were obtained from 76% of 350 device-associated samples yielding 237 bacterial isolates. Candida was isolated from 8.6% of these samples. Total Gram negative isolates predominated (n=216) comprising 91% of bacterial isolates and Gram positive 8.8% only of 237 isolates. Monomicrobial growth was found in 187 samples, dimicrobial in 26 and trimicrobial in 3 samples. Non lactose fermenters were 133 and fermenters 83. Acinetobacters sp. comprising 40%, Pseudomonas (22%), E coli (18.5%) and Klebsiella (16.6%)

Acinetobacters were the most drug resistant. A quarter were pan resistant, half were sensitive to one drug only mainly to imipenem. 21% were sensitive to two drugs. Three Acinetobacters were sensitive to 3 drugs. Totally 40% Acinetobacters were imipenem sensitive. Total and partial resistance was seen in 77% strains. Pseudomonas were 94% sensitivity to imipenem. Only 3.3% exhibited resistance to imipenem. Pan resistance was exhibited in 30 Gram negative strains with 4 ESBLs. **(Table 3)**

In 2015 a total of 446 samples were sent for culture sensitivity from ICUs of which 302 (67.7%) were of device-associated. Growth of 309 isolates was yielded from 219 (72.5%) samples. Coincidently in 2015 growth negative samples were 83 like 2010. Tracheal samples constituted 62.6% samples, non tracheal 37.4%, tips 90 (30%) samples, Folley's catheter were 13.**(Table1)** From 189 tracheal samples growth was obtained in 166 (54.5%) samples. No growth was obtained in 26 tracheal samples. From the 113 non tracheal samples 54 samples were growth positive and 59 growth negative. In 2015 Gram negative bacteria were 270 in number (87.4%) of the total 309 isolates. Non lactose fermenters constituted one large group of bacteria n=149 and comprised 55% of the total gram negative isolates, followed by lactose fermenters (n=119) comprising 44% of Gram negative isolates **(Table 2).** Gram positives constituted 12.6% and Candida 5.2% of the total isolates.

The total Acinetobacters isolated were 90 with 84.4% from trachea. Twenty of these were pan resistant, 43 sensitive to one drug mainly tigycycline, 17 sensitive to 2 drugs and 10 to 3 drugs. Likewise a quarter of Pseudomonas was pan resistant and 13 sensitive to one drug. Eighteen lactose fermenters exhibited pan resistance. Proteus and Citrobacter isolates have increased in number, in pan resistance and in ESBLs production **(Table-3)**. In total 53 pan resistant isolates with 14 ESBLs were recorded. Resistant bacteria n=66 (21.5%) were isolated from trachea only.

Table-1: Comparison of Type of Samples submitted to ICUs and their Culture results

Year	Total samples submitted	Device samples No.	%	Growth Positive No.	%	Growth negative No.	%	Tracheal samples No.	%	CV Tips No	%	Folley's Catheter No	%
2010	886	350	39.5	267	76	83	23.7	212	60	96	27	43	12
2015	446	302	67.7	219	72	83	27.4	189	62.6	90	30	13	4.3
Diff	440	48	04	48	04	0	3.7	23	06	06	03	30	7.7

Table-2: Bacterial Profiles in DAI Studies 2010 and 2015.

Samples				Gram Positive Bacteria					Gram Negative Bacteria											
Year	Device N	Growth %	No	ORSA No.	%	CONS	CONS	No	Acinet No.	%	Pseud. No.	%	E coli No	%	Kleb No	%	Prot. No	%	Citro. No	%
2010	267	76	21	05	24	07	08	216	86	40	47	21.7	49	18.5	36	16.6	08	3.7	01	0.5
2015	219	72	39	12	31	01	06	270	90	33	59	21.8	43	16	33	12	29	10.7	16	5.9
Diff	48	04	18	07	07	06	02	54	04	07	12	0	03	2.5	03	4.4	21	07	15	5.5

Table-3: Microbiological drug resistance patterns in the years 2010 & 2015.

Isolate	Total no 2010	Pan Resistant 2010		Single drug sensitivity 2010		Total no 2015	Pan Resistance 2015		Single drug Sensitivity 2015	
Acinetbacter	86	21	24.4%	45	Imp* 23	90	20	22.2%	43	tcg* 24
Pseudomonas	47	01	2%	10	Imp 09	59	15	25.4%	15	taz* 07
E coli	40	03	2 ESBL*	07	Imp 05	43	01	5 ESBL	05	imp/tgc
Klebsiella	36	04	2 ESBL	07	Imp 06	33	12	4 ESBL	15	imp 07
Proteus	07	01		01	Imp 01	29	04	4 ESBL	08	taz 04
Citrobacter	01					16	01	1 ESBL	12	tgc 07
S aureus	12	05	ORSA*			15	14	ORSA		
CONS	06	01	ORSS*			08	08			
	265	36	13.6%	70	26.4%	309	754	24.4%	96	31.3%

Table-4: Comparative studies for type of isolates.

Studies	Samples total no	Culture Positive		Gram Negative		Gram Positive		CONS		Fungi	
		No	%	No.	%	No	%	No	%	No	%
Polish 2016	206	200	70		46.5		53.	40	01	09	4.3
Irfan 2015	228	129	3.7	141	61.8	59	26	06	21	-	
Pak 2015	302	219	2.5	270	87.4	39	12.6	06	2.2	16	5.2
Pak 2010	350	267	6.2	216	81	21	7.9	08	2.9	30	1.2

Table-5: Comparative studies for Bacterial Profiles and Drug Resistance in Baseline Period and after Intervention.

Bacteria	Turkey		2013[15]		Cuba 2013[16]		5 Countries[17]		Pakistan			
	Pre n=65		Post n-394		Pre	Post	Pre	Post	Pre 2010[1] n = 350		Post 2015 n=302	
Ram negative	%	R	%	R	%	%	%	%	n	PanR%	N	PanR%
Acinetbacter	22	Imp78.3	33	Imp 64.4	100	07	2	18	86	24.4	90	22.2
Pseudomonas	32	Imp 43.3	30	Imp 40.6	00	36	57	55	47	2.1	59	25.4
E coli	09		05		00	14	07	18	40	12.5	43	13.9
Klebsiella	07		11		00	29	29		36	1636	33	48.5
Proteus	01		01						08	14.3	29	27.6
Citrobacter	20	80	-						01	4.5	16	14.9
S aureus ORSA	0		13	73.2		07	00	09	12	83.3	14	93
Staphylococci	03		01	ORSS*					06	16.6	10	80
Candida	03		01						30	-	16	-

Disucssion

ICUs harbour a dependant and immuno compromised population of patients who further have device dependency e.g. premature infants or with respiratory distress have endotracheal intubation and mechanical ventilation.[8] The altered host response plus large bacterial load with all types of pressures on bacteria by drugs, disinfectants in the milleu interior and exterior of the patient result in resistant strains. Further transmission of such strains to other patients by personnel and fomites, aid spread in hospitals. Thus resistant strains emerge, colonize, contaminate and infect the patients. These two studies were compared for any change in the pattern over a period of 5 years with implementation of Infection control MSDS Policy by Punjab Health Care Commission in the year 2014.

The total number of samples submitted to Microbiology laboratory has decreased drastically from 886 to 446. In 2015, a decrease of 440 samples submitted by ICUs was witnessed. The Foley's catheter samples also decreased by 44 samples. The total samples have decreased by 50% but device associated by 28%**Table 1.**

Table2 shows a greater number of device-associated samples in 2010 but in terms of percentage the difference is of 4%. This means with a 50% reduction in submitted samples the ratios of device associated samples are almost the same which shows high infection rates. All the microbial profiles have not changed much. *Proteus* spp and *Citrobacte*r spp isolation rates are on the increase. Candida isolation has decreased.

Table 3 is very significant. Resistance to antibiotics have increased as has pan resistance. In 2010, thirty six pan-resistant strains were isolated and in 2015 their number has increased to 75 in 2015. An increase from 13.6% to 24.4%.There is a decrease in *Acinetobacter* resistance by 2% but an increase in *Pseudomonas* pan-resistance from 2 to 24% in 2010 & 2015 respectively. Likewise ESBLs increased from 4 to 14 in Enterobacteriaceae. They were only seen in *E coli* and *Klebsiella* spp. Now they are found in *Proteus* and *Citrobacter* too.**(table3)** The developed countries maintain data base on device-associated healthcare associated infection [DAHAI] in ICUs. Surveillance is pivotal in infection control practices and quality assurance [12] The incidence rate of DAIs decreased in ICUs after establishment of Korean Nosocomial Infection Surveillance Systems [KONIS] in 2006. Like ventilator associated pneumonia [VAP] rate per 1000 ventilator days from 3.48 to 1.93.[3]

The focus of hospital infection is the surgical and allied theatres. ICUs should be targeted more than the theatres as they are a perpetually ill segment of patients who are device dependant. Ventilators are open channels for all saprophytic bacteria like *Acinetobacters* and *Pseudomonas*. Compared to close channel devices the ventilator associated infections are more in number.

Inexpensive preventive strategies can be made as avoidance of devices until mandatory, daily anti-sepsis of oral area, intra venous devices and catheters. Earliest possible removal of devices, disinfection of environment, hand hygiene, waste management, Antibiotic Stewardship Programmes all may help in circumventing DAIS in ICUs.

International Nosocomial Infection Control Consortiu (INICC) is an international non profit, open, scientific community that works interactively through a network that aims at reducing hospital acquired infections, mortality, bacterial resistance, length of stay in hospital and thus extra cost. INICC in developing countries helps in global surveillance programmes based on Centre for Disease Control (CDC) and Prevention's National Healthcare Safety Network (NHSN) and provide guidelines with basic and inexpensive tools and resources for systematic control and prevention of nosocomial infection.[1,14,15,16]

INICC was started in 1998 by Dr Victor D Rosenthal. In 1993 he joined doctors National Infection Control Guidelines in Argentina; Infectious Disease Society of Argentina; but non compliance followed. So multinational surveillance and research was started on voluntary basis to asses the magnitude of infection problems, their risks and translation to economic burdens. With this risk factors and cost effectiveness were highlighted and compliance improved[1] In US for over 50 years, CDC methods are applicable for measuring nosocomial infection. With this infection control and prevention guidelines were laid. Infection rate differs by ratio of 1:5. Now it has become a multi-centric organization with 2000 healthcare centres voluntarily joined in 500 cities, 66 countries and 4 continents. Confidentiality of the healthcare set-up is maintained. There are two phases of studies, phase 1 baseline period of participation in INICC programme and phase 2 the intervention period.[14]

All the above stated studies describe the impact on bacteria after interventions.

Studies are mostly from developing countries. Studies report decrease in bacteria after interventions. The Turkish study seems to have increased number of bacterial isolates post intervention but the number of samples have also increased six-fold (ie from n=65 to n=365) in 3 months interval. The total number of samples have increased over 5 years by 48 in our study. However it records a significant increase in isolation of *Pseudomonas, Proteus, Citrobacter*. Moreover pan-resistance also increased tremendously by Pseudomonas (6.3%) Klebsiella four fold (16.6%-48.5%), Proteus by 13.3%, *Citrobacter* by 10%. Also gram positive MRSA isolates were increased by 51% and coagulase negative staphylococci by 83%. The increase in bacteria and their pan resistance just reflects that there is need of affiliation with INICC and educational interventions for systematic infection control as per guidelines are mandatory. Current infection control practices need to be improved. All this is aimed at patient and state welfare which would reduce the nation's economic burden of health.

Conclusion

DA-HAIs are a serious threat in hospitals to all patients but more so in ICUs. A database should be maintained for infection in ICUs. National Surveillance Programmes should be carried out and

linked to INICC or CDC to follow their guidelines for infection control in our hospitals too like the developed nations. This would decrease DAIs and translated in decrease in economic expenditure by less antibiotic use, short hospital stay, less morbidity and mortality.

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Original Article

Frequency of Thyroid Dysfunction in Patients of Chronic Hepatitis C Treated with Interferon Alpha 2B and Ribavirin

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Objective: To determine the frequency of thyroid dysfunction in patients of chronic hepatitis C treated with Interferon alpha 2b and Ribavirin.

Methods: A total of 120 cases having active hepatitis C assessed by HCV RNA PCR as per operational definition for atleast 3 months between 15 years to 60 years of both gender were included in the study from outdoor of Services Hospital Lahore after a written informed consent. All the demographics including name, age, gender and address were entered in a pre-defined questionnaire. Patients were treated with Interferon alpha 2b (dose) three million international units subcutaneously three times a week and Ribavirin (dose) 1200 mg oral daily for 24 weeks. As per hospital routine Thyroid dysfunction was evaluated as per operational definitions by collecting 4ml of blood in a 5cc syringe at 0 (baseline) and 12 week. Presence or absence of thyroid dysfunction at 12 weeks was labelled as per operational definition.

Results: In our study, out of 120 cases, 42.5%(n=51) were between 15-40 years while 57.5% (n=69) were between 41-60 years of age, mean±sd was calculated as 42.49±11.54 years, 59.17% (n=71) were male while 40.83% (n=49) were females, frequency of thyroid dysfunction in patients of chronic hepatitis C treated with interferon alpha 2b and ribavirin was recorded in 21.67% (n=26).

Conclusion: We concluded that the frequency of thyroid dysfunction in patients of chronic hepatitis C treated with Interferon alpha 2b and Ribavirin is not very high but reaches at a considerable level and necessary steps should be taken for the management of this morbidity while interferon therapy is given to the Hepatitis C virus cases.

Keywords: Chronic hepatitis C, treatment, interferon alpha 2b and ribavirin, thyroid dysfunction.

Introduction

Globally, the hepatitis C virus (HCV) has infected an estimated 170 million people, most of whom are chronically infected with a high risk of cirrhosis and hepatocellular carcinoma and they serve as a reservoir for transmission to others.[1] Interferon-alpha (IFN-α) based antivirus therapy, regular IFN-α or pegylated Interferon alpha in combination with Ribavirin, is recognized as being a highly effective treatment for patients with chronic hepatitis C (CHC).This therapy results in a sustained virological response (SVR) in 4050% of patients with genotype 1, and around 80% in those infected with genotype 2 and 3.[2]

Despite their favourable efficacy, these IFN-α based regimens are also accompanied by many well-known adverse effects, including; fever, depression, anemia, neutropenia, thrombocytopenia and endocrine side effects.[3] The most commonly documented extra hepatic endocrine side effect of these IFN-α based regimens is the production of auto antibodies and the development of thyroid dysfunction (TD).

Retrospective analysis of 109 HCV-treated patients (for 6 to 12 months, according to HCV genotype) for the period 1996 to 2008. Thyroid function tests were performed every 3 months during therapy and after discontinuation (3 months to 12 years). Routine laboratory tests and virological assessment were performed according to generally accepted practice. TD was observed in 26 patients (23.85%) who were treated with Interferon alpha-2b (3 million international unit) subcutaneously three times a week and Ribavirin oral 1200mg daily.[4]

One hundred cases of CHC, proven by anti-HCV and HCV RNA-positive with baseline TSH, FT4 and FT3 within the normal reference range, who were treated with interferon alpha-2b (3 million international unit subcutaneously three times per week) and oral ribavirin (1000-1200 mg per day) were included in this study. All patients were assessed for TSH, FT4, FT3 levels at 12 weeks and 24 weeks during therapy. Among the 100 patie ts, overt thyroid disease developed in13 (13%) and sub-clinical thyroid disease

in 5 (5%). Out of 13 patients of overt thyroid disorders, 11 (84.6%) had hypothyroidism and 02 (15.3%) hyperthyroidism. Four (80%) patients were of sub-clinical hypothyroidism and 01 (20%) patient was of sub-clinical hyperthyroidism. Overall, thyroid disorders developed in 18 (18%) both as overt and sub-clinical thyroid disorders.[5] In another study in which both drugs were given to a single patients thyroid dysfunction (TSH <0.1 or >5 mU/L) had developed in 58 patients (12.6%).[9] One hundred and sixty seven non-cirrhotic chronic hepatitis C patients were grouped into treatment group (n=107) and control group (n=60) awaiting treatment. Baseline serum (s) Alanine Transferase (ALT) and S. Aspartate Transferase (AST) were measured by IFCC method. Serum Thyroid Stimulating Hormone (S. TSH), serum free thyroxine (S. Free T4) and serum total triiodothyronine (S.T3) level were determined by chemiluminescence. Study group patients underwent 24 weeks Interferon and Ribavirin therapy and were followed-up for thyroid dysfunction at weeks 0, 12 and 24. Control group patients underwent the same tests at weeks 0, 12 and 24. Out of 107 patients of treatment group, 20 patients (18.69%) developed thyroid dysfunction whereas only one patient developed TD in control group out of 60 patients.[6]

The rationale of this study is to determine the actual frequency of thyroid dysfunction in patients using Interferon and Ribavarin. There are controversial results in the literature[6,7] so this study will clarify the results. Moreover there was no local study available on effect of interferon on thyroid function and ethnicity also has impact on frequency as stated by Mameen JS[8] so this will reveal us weather we have to consider TD in our population before advising these medications in patients of Chronic Hepatitis C.

Methods

Study was conducted in Medical unit M-IV Services Hospital, Lahore. It is descriptive case series.

The sample size estimated is 120 using 95% confidence level with 7% margin of error with an expected percentage of thyroid dysfunction as 18%.Ptients of both genders between 15 years to 60 years and patients having active hepatitis C assessed by HCV RNA PCR as per operational definition for atleast 3 months. Patients who had any type of throat surgery. e.g Thyroidectomy Patients or with thyroid abnormality before onset of treatment.e.g Hyperthyroidism or Hypothyroidism as per operational definition and Patients with diabetes mellitus (Previous medical recoror who had taken treatment for Hepatitis C were excluded.

After fulfilling inclusion and exclusion criteria a total of 120 patiets presenting in outdoor of Services Hospital Lahore who have chronic hepatitis C as per operational definition were enrolled in this study after a written informed consent. All the demographics including name, age, gender and address were entered in a pre-defined questionnaire. Patients were treated with Interferon alpha 2b (dose) three million international units subcutaneously three times a week and Ribavirin (dose) 1200 mg oral daily for 24 weeks. As per hospital routine Thyroid dysfunction was evaluated as per operational definitions by collecting 4ml of blood in a 5cc syringe at 0 (baseline) and 12 week. Presence or absence of thyroid dysfunction at 12 weeks was labelled as per operational definition.

Data was entered on computer software SPSS version 17. Quantitative data like age, TSH and T3 levels were presented by mean and standard deviation while qualitative data like gender and thyroid dysfunction was presented by frequency and percentages. Data was stratified for age, gender, duration of Hepatitis C to deal with effect modifiers. Poststratification Chi-square test was applied. P-value ≤ 0.05 was considered significant.

Results

A total of 120 cases fulfilling the inclusion/exclusion criteria were enrolled to determine the frequency of thyroid dysfunction in patients of chronic hepatitis C treated with Interferon alpha 2b and Ribavirin. Age distribution of the patients was done showing that 42.5%(n=51) were between 15-40 years while 57.5%(n=69) were between 41-60 years of age, mean+sd was calculated as 42.49±11.54 years. **(Table1)** Patients were distributed according to gender showing that 59.17%(n=71) were male while 40.83%(n=49) were females. **(Table-2)** Mean TSH and T3 levels were calculated as 3.29±2.44 and 144.98±49.45.

(Table-3) Frequency of thyroid dysfunction in patients of chronic hepatitis C treated with interferon alpha 2b and ribavirin was recorded in 21.67%(n=26) while 78.33%(n=94) had no findings of the morbidity. **(Table-4)** Stratification for frequency of thyroid dysfunction in patients of chronic hepatitis C treated with interferon alpha 2b and ribavirin age, gender and duration of hepatitis C virus were recorded and presented in **(Table- 5,6,7)**

Table-1: Age distribution (n=120).

Age (in years)	No of Patients	Percentage
15-40	51	42.5
41-60	69	57.5
120	120	100
Total	Coma	3
Mean±sd	42.49±11.54	

Table-2: Sex distribution (n=120).

Age (in years)	No of Patients	Percentage
Male	71	59.17
Female	49	40.83
Total	120	100

Table-3: Mean TSH and T3 Levels (n=120).

TSH/T3	Mean	Percentage
TSH	3.29	2.44
T3	144.98	49.45

Table-4: Frequency of thyroid dysfunction in patients of chronic hepatitis c treated with interferon alpha 2b and ribavirin (n=120).

Thyroid dysfunction	No. Of Patients	Percentage
Yes	26	21.67
No	9	78.33
Total	120	100

Table-5: Stratification for frequency of thyroid dysfunction with regards to age.

In Years	Thyroid dysfunction (N=26)		P-value
	Yes	No	
15-40	08	43	0.17
41-60	18	51	

Table-6: Stratification for frequency of thyroid dysfunction with regards to gender.

Gender	Thyroid dysfunction (N=26)		P-value
	Yes	No	
Male	15	56	0.86
Female	11	38	

Table-7: Stratification for frequency of thyroid dysfunction with regards to duration of hepatitis c.

Duration of hepatitis C	Thyroid dysfunction (N=26)		P-value
	Yes	No	
1-3 Years	12	42	0.86
>3 years	14	52	

Discussion

Hepatitis-C virus infection is a worldwide problem and its natural, unfavorable course is still a challenge for the hepatologist. The standard of treatment is combined therapy with interferon-alpha and ribavirin. Treatment of hepatitis-C infection often results in many endocrinological disturbances of which thyroid dysfunction is most prevalent1. Interferons are a family of naturally occurring, small protein molecules with molecular weight of 15,000-20,000 Da. They are included in three groups, IFN alfa, IFN-beta, IFN-gamma with different biological effects and variable duration of activity. Ribavirin is a synthetic Guanoside nucleoside analogue that exerts immuno modulatory effects by inducing cytokines in the against HCV infection and is frequently given with IFN in the treatment of chronic hepatitis C patients. A high prevalence of thyroid gland dysfunction has been reported in hepatitis C virus (HCV) infected patients before and after interferon Alfa therapy and some data also show a high prevalence of anti-HCV antibody in patients with autoimmune thyroiditis.

We planned this study with the view to determine the actual frequency of thyroid dysfunction in patients using Interferon and Ribavarin due to the fact that there are controversial results in the literature[6,7] so this study may clarify the results.

In our study, out of 120 cases, 42.5%(n=51) were between 15-40 years while 57.5%(n=69) were between 41-60 years of age, mean±sd was calculated as 42.49±11.54 years, 59.17%(n=71) were male while 40.83%(n=49) were females, frequency of thyroid dysfunction in patients of chronic hepatitis C treated with interferon alpha 2b and ribavirin was recorded in 21.67%(n=26).

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One hundred cases of CHC, proven by anti-HCV and HCV RNA-positive with baseline TSH, FT4 and FT3 within the normal reference range, who were treated with interferon alpha-2b (3 million international unit subcutaneously three times per week) and oral

ribavirin (1000-1200 mg per day) were included in this study. All patients were assessed for TSH, FT4, FT3 levels at 12 weeks and 24 weeks during therapy. Among the 100 patients, overt thyroid disease developed in 13 (13%) and sub-clinical thyroid disease in 5 (5%). Out of 13 patients of overt thyroid disorders, 11 (84.6%) had hypothyroidism and 02 (15.3%) hyperthyroidism. Four (80%) patients were of sub-clinical hypothyroidism and 01 (20%) patient was of sub-clinical hyperthyroidism. Overall, thyroid disorders developed in 18 (18%) both as overt and sub-clinical thyroid disorders.[5] In another study in which both drugs were given to a single patients thyroid dysfunction (TSH <0.1 or >5 mU/L) had developed in 58 patients (12.6%).[9] these findings are significantly lower than our study, we could not identify any reason for this difference. One hundred and sixty seven non-cirrhotic chronic hepatitis C patients were grouped into treatment group (n=107) and control group (n=60) awaiting treatment. Baseline serum (s) Alanine Transferase (ALT) and S. Aspartate Transferase (AST) were measured by IFCC method. Serum Thyroid Stimulating Hormone (S. TSH), serum free thyroxine (S. Free T4) and serum total triiodothyronine (S.T3) level were determined by chemiluminescence. Study group patients underwent 24 weeks Interferon and Ribavirin therapy and were followed-up for thyroid dysfunction at weeks 0, 12 and 24. Control group patients underwent the same tests at weeks 0, 12 and 24. Out of 107 patients of treatment group, 20 patients (18.69%) developed thyroid dysfunction whereas only one patient developed TD in control group out of 60 patients.[6] These findings support our results.

However, the findings of our study may be among the primary data in our population and some other studies may be done to determine this frequency in other parts of our country.

Conclusion

We concluded that the frequency of thyroid dysfunction in patients of chronic hepatitis C treated with Interferon alpha 2b and Ribavirin is not very high but reaches at a considerable level and necessary steps should be taken for the management of this morbidity while interferon therapy is given to the Hepatitis C virus cases.

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Original Article

Reasons for Cancellation of Operation in a 235 Bedded Public Sector Hospital Dedicated for Gynaecology and Obstetrics in Lahore

Muhammad Imran Azeem, Muzammil Hussain, Jodat Saleem and Kashif Mumtaz

Objective: To evaluate the reasons for cancellation of elective surgical operation of the patients who presents for pre-Anaesthesia evaluation one day before surgery or on the day of surgery in a 235 bedded public sector hospital in Lahore..

Methods: The medical records of all the patients, from 1st June 2014 to 30th May 2015, who had their operations cancelled one day before surgery or on the day of surgery in all gynaecology and obstetrics units of the hospital, were audited prospectively. The number of operation cancelled and reasons for cancellation were documented in detail.

Results: 2160 patients were scheduled for elective surgical procedures during the study period of one year; 204 (9.4 %) of these were cancelled one day before surgery during pre-Anaesthesia fitness or on the day of surgery. The most common cause of cancellation was inadequate patient preparation. 59 (28.92%) patients were cancelled as they were not adequately prepared for surgery as per anesthetist advice (incomplete NPO, Investigations or referrals required). The second most common cause of cancellation was the un optimized medical status of the patients53 (25.98%). 36(17.65%) cancellations were because of equipment failure/Electricity shutdown; 17 (8.33%) cancellations due to lack of operation theater time; 16 (7.85%) were cancelled due to patient's refusal/patient left against medical advice; 12 (5.88%) were cancelled by the surgeon due to a change in the surgical plan and 11 (5.39%)patients were cancelled due to non-availability of surgeon.

Conclusions: Most causes of cancellations of operations are preventable.

Keywords: Cancellation, elective surgical operations, gynaecology and obstetrics.

Introduction

Operation theater is the prime and most sensitive area of any hospital in terms of human resources and finances from hospital budget. However, most of the time operation theaters are underutilized and are unable to give their maximum output in accordance to their actual functioning capacity. At times patients scheduled for surgeries from elective and waiting list are postponed.[1,2] A significant amount of hard work is required to prepare the patients for an elective surgical procedure pre operatively. This includes the review of patient notes, necessary Investigations, consultant advice. At the same time OT staff must ensure the availability of surgical instruments, monitors, drugs and linen. The ward staff should feel responsible regarding the preparation of the patient shifting to operation theaters according to scheduled operation list. Last minute cancellations result in inefficient use of resources, not in the interests of the patient or the hospital, and result in anxiety, agitation and financial loss to the family and hospital.[3]

Cancellation of elective operations reflects the in efficient quality care and poor management. The reported incidence of cancellation in different hospitals ranges from 10% to 40%. There are many reasons of cancellation of elective surgical cases; and they differ from hospital to hospital.[4]

Un-anticipated operating room (OR) cancellations are divided into avoidable cancellations (e.g., scheduling errors, equipment shortages, and inadequate preoperative evaluation) and unavoidable cancellations (e.g., emergency cases, unexpected changes in the patient's medical status, or patient non appearance). The most common cause of cancellation of surgical procedure is lack of OR time.[4] The aim of this prospective study was to analyze the causes of cancellation of elective surgical procedures in a mono disciplinary 235 bedded government hospital and to suggest measures for optimal utilization of or time.

Methods

All the patients scheduled to undergo elective surgical procedures, between 1st May 2014 to 30th June 2015

were include in the study at Lady Walingdon Hospital, Lahore. This is tertiary care 235 bedded hospital dedicated for gynaecology & obstetric patients. Patients were included prospectively in the study. As this study was considered as audit under quality assurance project, it did not require approval of the hospital ethics committee. A formal pre anesthesia assessment was carried out on every patient a day before surgery scheduled in MOT undergoing general anaesthesia, monitored anaesthesia care or neuraxial blocks. The preoperative assessment of the patients referred from surgical wards, labour rooms or unit ICUs was done in the preoperative holding area. The preoperative assessment was carried out in the structured manner on specially designed Performa of pre anaesthesia assessment. The patients were assigned ASA (American Society of Anaesthesiologists) risk score after pre-operative assessment and review by the consultant if required. All ASA 3 or higher patients were examined by the anaesthesia consultant before declaring her fit or unfit for surgery. Special investigations, referrals, delays, postponement or need for blood/blood products were advised after discussing with the consultant in charge. Final decision regarding postponement or cancellation was given after mutual consultation between anaesthesia and surgical consultant.

On the day of intended surgery, all the patients were shifted to the preoperative area in the morning after 8 AM. In the preoperative holding area, the anaesthesia medical officer reviewed the vital signs, GCS, current medications. Patients of ASA class III and above were re-examined and their charts for current status of disease were also reviewed along with NPO status. The anaesthesia consultant confirmed with the medical officer in case there is a change in medical status of the patient after re examination and investigation review. All the patients who did not declared fit for surgery were documented in "Postponed Patients Record" register dedicated for this study. The patient and family were counseled regarding the change in the status and postponement. All the changes in status, postponement, further treatment, referral or future anaesthesia plan were documented with date and time. Data on operations were obtained from the OT register maintained by the OT incharge nurse in which surgical record were written including patient and surgeon details along with intended procedure.

Cancellations were classified as:

- Potentially avoidable reasons could be due to failure to adequately prepare the patient. (Poorly scheduled OT timings, lack of postoperative beds, list error, administrative cause, equipment or transport problem, communication failure, patients medical condition not optimized, and surgeons un availability in O.R).
- Non avoidable reasons which were outside the control of hospital staff, such as that the patient did not follow the NPO advise, refusal by patient, patient clinical status change, emergency priority etc.

As this classification was based on the detailed reason given for the cancellation, some of the three major categories appear in both the avoidable and unavoidable groups.

Patients factors = Patients having medical. problems, inadequate preparation, incomplete NPO and refusal etc.

Manpower factors = Lack of availability of medical and paramedical staff.

Hospital factors = Equipment failure, lack of surgical instruments or linen and interruption in electric power supply or generator malfunction and lack of operation theater time.

Results

A total of 2160 patients were scheduled for elective surgical procedures during the one year of study period. The total number of surgical operations performed was 1956. The total number of patients cancelled was 204 (9.4 %). These patients were cancelled one day before surgery during pre-Anaesthesia fitness or on the day of surgery. The most common cause of cancellation was inadequate patient preparation. 59 (28.92%) patients were cancelled as they were not ready for surgery.

The various causes in this most common category included incomplete NPO, Investigations or referrals required. The second most common cause of cancellation was the patient's medical condition including 53 (25.98%) patients who were cancelled for surgery due to uncontrolled hypertension, uncontrolled blood sugar levels due to diabetes mellitus, active respiratory tract infections and other various medical conditions. 36 (17.65%) cancellations were because of equipment failure/Electricity shutdown which included Anaesthesia machine malfunction or failure, oxygen supply interruption, lack of surgical instruments or linen and interruption in electric power supply or generator malfunction. 17 (8.33%) cancellations due to lack of operation theatre time which is usually ends at 2:00 PM daily and 12:00 Noon at Friday. 16 (7.85%)

were cancelled due to patient's refusal/patient left against medical advice.

12 (5.88%) were cancelled by the surgeon due to a change in the surgical plan and 11 (5.39%) patients were cancelled due to non-availability of surgeon. **(Table.1,2)** shows whether the reason of postponement of surgery was avoidable or unavoidable. In our study 60.29% cancellations (N=123) were avoidable, while 39.71% (N=81) cancellations were unavoidable. The hospital has 3 gynaecology units (Unit 1, 2 and 3). As per hospital routine, two elective surgical lists are performed every week by each unit from Monday to Saturday with 3 days gap in between their surgical list. Therefore every patient who was cancelled from elective surgical list had to face the delay of at least 3 days to be re-scheduled on next surgical list. In our study, the average delay faced by the cancelled patients was 6.26 days with the range of 3 days to 14 days. The proportion of cancelled patients during study period was 29.41% (n=60), 36.76% (n=75) and 33.83% (n=69) from Unit 1, 2 and 3 respectively.

The factors contributed in cancellation included:

Patients factors = 68.63% (n=140). Patients having medical problems, inadequate preparation, incomplete NPO and refusal etc

Manpower factors= 5.39% (n=11). Lack of availability of medical and paramedical staff

Hospital factors= 25.98% (n=53). Equipment failure, lack of surgical instruments or linen and interruption in electric power supply or generator malfunction and lack of operation theater time .

Table-1: Reasons for cancellation of surgery.

Factors attributed for cancellation	Reasons of cancellation		No. Of Patients	Cancellation (%)	Cancellation Avoidable/ Unavoidable
Patient factors	Patients not prepared	Investigations required	23	11.27%	Avoidable
N=140	N=59	Referral required (Med. Surg. Or others)	28	13.73%	Avoidable
68.63%	28.92%	Incomplete NPO	08	3.92%	Avoidable
	Medical Reasons	Uncontrolled HTN	38	18.63%	Unavoidable
	N=53	Uncontrolled DM	09	4.41%	Unavoidable
	25.98%	RTI & Others	06	2.94%	Unavoidable
	Surgical Reasons	Change of surg. Plan	12	5.88%	Unavoidable
	Patients refusal /LAMA		16	5.85%	Unavoidable
Hospital factors	Equipment failure/electricity shutdown		36	17.65%	Avoidable
N-53 25.98%	Lac of OT Time		17	8.33%	Avoidable
Manpower factors	Surgeon not available		11	5.39%	Avoidable
N-11 5.39%	Anaesthetist not availble		0	0%	-

Table-2: Avoidable / Non Avoidable factors for postponement of surgery.

	Potentially avoidable	Unavoidable
Patient factors n=140 68.63%	N=59 42.14%	N=81 57.86%
Hospital Factors n=53 25.98%	N=53 100%	-
Manpower factors n=11 5.39%	N=11 100%	-
Total n=204	N=123 60.29%	N=81 39.71%

Discussion

For a well organized surgical care in a tertiary care hospital there should be a low rate of cancellation of surgical procedures. The postponement of elective surgeries results in underutilization of facility and the efficiency of the operation theaters will be compromised. As a result the number of patients will keep on increasing on the waiting list and hence will result in an increase financial burden on the patients and families.[1]

This is a known fact that underutilization of resources will have a direct impact on the lower income groups. These low socio economic groups in third world countries are dependent for their health care services primarily on public sector hospital. So if a facility or theater equipment in a public sector hospital is not utilized to its full extent, the ultimate cost will be beard by the patients. So the most important step is to avoid postponement of the patients on elective surgical list.

The National Audit Office in Britain reviewed five district health authorities, and concluded that OTs

were not used even half of their capacity instead of long waiting lists.[1,5] The undue postponements may results in financial burden and psychological distress for the patients and the families. Mostly the elective surgical procedures are cancelled on 24-hour notice. The patients and the families feel apprehensive, scared, dishearted and bitter. Even in developed countries like UK, 8% of scheduled elective surgeries are cancelled.[1]

Conclusion

This audit found that most of the causes of cancellation of operations are avoidable. Careful patient preparation can significantly reduce the un-anticipated cancellation of elective operation list. Before formation of OT list, current existing limitations in human and material resources should be kept in consideration so that under-utilization of existing resources can be minimized due to unwanted cancellation.

The medical problems requiring consultation or referral can be identified before time by careful history taking and examination at the time of admission. The number of cancellations on medical grounds can be minimized by giving proper attention to the patient's other medical conditions in addition to the specific surgical cause for which patient had admitted. The compliance and effectiveness of the medical treatment being given in the surgical ward can be assessed by repeated medical consultation/ referrals. The patients requiring medical optimization should not be re-scheduled immediately without waiting for the medical problems to get optimized.

To avoid under or over utilization of OT facilities, number of patients enlisted in OT list should be justified according to the capacity of various OT facilities.

The malfunctioning of equipment or non-availability of drugs or others instruments necessary for scheduled surgical list should be should be identified reasonably before time by the responsible persons. If the equipments or manpower limitation created temporarily, it should be informed timely to concerned people prior to preparation of OT list.

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Original Article

Correlation of Anthropometric Parameters to Severity of Hirsutism in Women

Muhammad Sohail Aslam, Shumaela Kanwal And Hamid Javaid Qureshi

Objective: To investigate the relationship between the anthropometric parameters and the severity of hirsutism.

Methods: A sample of sixtyfemale subjects, aged 18-35 years,having hirsutism was selected, while ten normal healthy females were randomly included as controls.Height, weight and waist circumference of subjects were measured.Body mass index (kg/m2) was calculated. All subjects underwent an assessment of excess terminal hair growth using the modification of the method originally described by Ferriman and Gallwey (FG). Hirsutism was classified as mild (score 8-15), moderate (score16-25), and severe (score >25).

Results: The mean SD waist circumference, weight and body mass index values in hirsute subjects were significantly higher ($p < 0.05$) than those in controls. Significant positive correlations were observed between body weight, BMI and mild hirsutism score. However in moderate hirsutism, Ferriman Gallwey score was significantly and positively correlated with body mass index only.

Conclusion: The excess terminal hair growth is more common in overweight women having less hirsutism score.

Keywords: Hirsutism, body mass index ,modified ferriman-gallwey score.

Introduction

Structurally, there are three types of hair: lanugo is a soft hair densely covering the skin of the fetus, which disappears within the first few months of post-partum life; vellus hair are soft but longer than lanugo hair and areusually non-pigmented; and terminal hair which are longer, pigmented and coarser in texture. Eyebrows, eyelashes, scalp hair and pubic and axillary hair in both sexes, and much of the body and facial hair in men, are composed of terminal hairs.[1] Hirsutism refers to the presence of excessive terminal (coarse) hair in androgen-dependent areas of the female body. Its medical importance is highlighted by the high prevalence of androgen excess disorders reported among hirsute women.[2]

In 1961, Ferriman and Gallwey proposed a method to quantify the excessive hair growth in females.[3] This original method was modified in 1981 by Hatch *et al* and has now become the gold standard for the evaluation of hirsutism. This method scores nine body areas (upper lip, chin, chest, upper and lower back, upper and lower abdomen, arm, forearm, thigh and lower leg). Total score ranges from 0-36.[4]

Adipose tissue contributes up to 50% of the circulating testosterone in premenopausal women because of excessive androgen production in fat tissue.[5] Therefore, it seems that hirsutism must be more common in people with simple obesity but controversies exist. The aim of this study was to determine the anthropometric profile of women with hirsutism and correlate it with severity of hirsutism.

Methods

Study Design:

This case control study was conducted at the Institute of Molecular Biology & Biotechnology, University of Lahore, on sixty hirsute female subjects and ten normal healthy females aged 18-35 years.

Inclusion criteria:

Inclusion criteria taken into consideration were age (18-35 years)and clinical criteria. The clinical criteria were as follows:

- All patients of hirsutism with modified Ferriman-Gallwey (mF-G) score of eight or more were included in the study.
- Patients presenting with oligo/amenorrhea, ovulatory dysfunction, excess hair growth, virilization, alopecia, or acne.

Exclusion criteria:

- Pregnant or lactating women.
- Those who received oral contraceptive pills or/and other anti-androgen drugs in previous three months.
- Those who received drugs known to cause hirsutism or interfere with the hormonal studies.
- Patients with modified Ferriman-Gallwey (mF-G) score less than 8.

Study Protocol

The study was approved by the Ethical Review Committee of the Institute of Molecular Biology & Biotechnology, University of Lahore.

Initial subject evaluation:

All the subjects completed a standardized history and clinical proforma, including questions about age, family history of hirsutism, onset and duration of the disorder, marital status, menstrual cycle length and regularity, other illnesses, and medications.

Physical Examination

The following parameters were recorded:

Height (in centimeters without shoes against wall-fixed tape), weight (in kilograms with light cloths and without shoes), and waist circumference (in centimeters with the tape placed horizontally between the costal margin and iliac crest while the participant gently exhaled) were measured.

All the subjects also underwent an assessment of excess terminal hair growth using the previously described modification of the method originally described by Ferriman-Gallwey (i.e. mF-G), scoring the presence of terminal hairs over nine body areas (upper lip, chin, chest, upper and lower abdomen, thighs, upper and lower back, and upper arms). Hirsutism was classified as mild (score 8-15), moderate (score16-25), and severe (score >25). The nurses made the initial assessment, after being trained on the use of the scoring system by the principal investigator. Body mass index (kg/m2) was derived, using the formula:[6] Body mass index = Body weight (kg)/ Height (m)2.

The normal range of BMI was taken as 18-24.9 Kg/m2. Women with BMI 25-29.9Kg/m2 were labeled overweight and those having 30Kg/m2 or more were labeled obese.[7]

Data Analysis:

The demographic variables were presented as simple descriptive statistics calculating mean and SD of numerical data like age, duration of disorder, waist circumference, body mass index (BMI), and modified Ferriman-Gallwey (mFG) scores of hirsutism. The significance of difference between the groups was analyzed by independent samples Student's t-test and Pearson's correlation coefficient was determined to find out correlation. Ap value < 0.05 was considered statistically significant. All statistical analyses were carried out with the SPSS version 17 (SPSS, Inc, Chicago, IL, USA).

Results

Sixty hirsute female subjects were enrolled in this study. Their ages ranged from 18-35 years with a mean age of 24.58± 0.57 years. All were evidently hirsute in various degree of the disorder. A batch of ten female subjects of matching age with a mean value of 25.6 ± 1.76 years were also enrolled in study as the control group. About 25% of the subjects had the hirsute symptoms for shorter duration i-e up to maximum of 5 years and less. The rest had the disorder more than 5 up to 11 years. The duration of the disease ranged from 1-14 year. Family history of hirsutism was positive in12 (20%) patients. There was history of regular menstrual cycle in 47 patients (78.33%) and irregular menstruation in 13 patients (21.66%).

The mean waist circumference, weight, and body mass index (BMI) of the hirsute group were significantly more than the values in the control group. **(Table I).**

A total of 33 subjects had BMI in the normal range (18-24.9 Kg/m2). 16 subjects had BMI in the overweight range (25-29.9 Kg/m2). Out of these, 15 subjects had mild hirsutism and 1 subject had moderate hirsutism. 11 subjects had BMI in the obese range (25-29.9 Kg/m2). Out of these, 4 subjects had mild hirsutism and 7 subjects had moderate hirsutism. **(Table II).** Body weight and body mass index were significantly and positively correlated with mild hirsute subjects having mF-G score of 8-15 ($r = 0.49$; $p < 0.05$, $r = 0.50$; $p < 0.05$).**(Table III. Figures 1 & 2).**

Table-1: Anthropometric features of subjects in the control and hirsute groups.

Parameter	Hirsutes Mean±SD	Controls Mean±SD	P-value
Weight (cm)	88.92±74	81.00±7.2	0.003*
Weight (kg)	63.08±9.93	56.50±8.0	0.054*
Height (cm)	162.22±3.4	163.30±4.6	0.400
BMI (kg/m^2)	23.93±3.43	21.2.±2.11	0.015*

*(*p< 0.05, Statisticallysignificant)*

Table-2: BMI subgroups having mild and moderate hirsutism.

BMI	N	No of pts. having mild Hirsutism (Mean±SD)	No. Pts.having moderate Hirsutism (Mean±SD)
Normal (18.0-24.9 Kg/m2)	33	32 (9.69±1.77)	1 (16±0.00)
Overweight (25.0-29.9 Kg/m2)	16	15 (11.00±2.28)	1 (16±0.00)
Obese (30.0 Kg/m2or more)	11	4 (13.75±2.55)	7 (16.85±0.69)

In moderate hirsute subjects having mF-G score of 16-25, a significant and positive correlation was seen only between body mass index and moderate hirsutes($r = 0.62; p = 0.03$). **(Table IV. Figure 3).**

Table-3: Correlation of mild hirsutism with anthropometric parameters.

Mild Hirsutism	Correlation coefficient (r)	P-value
Waist circumference	0.231	0.107
Wight	0.498	0.001*
Height	0.106	0.463
Body Mass Index	0.506	0.001*

*(*p< 0.05, Statistically significant)*

Table-4: Correlation of moderate hirsutism with anthropometric parameters.

Moderate Hirsutism	Correlation coefficient (r)	P-value
Waist circumference	0.040	0.914
Wight	0.601	0.066*
Height	0.099	0.785
Body Mass Index	0.626	0.035*

*(*p< 0.05, Statistically significant)*

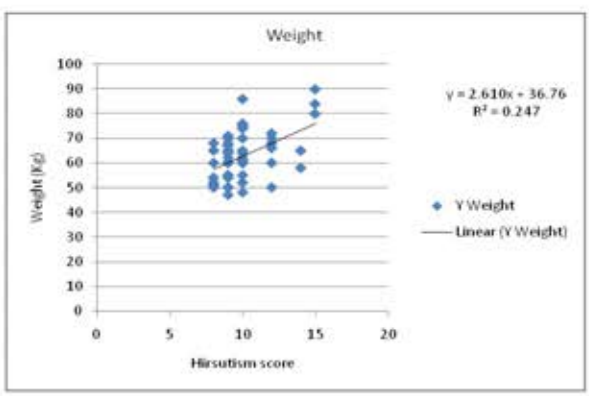

Fig-1: Correlation of weight with mild hirsutism.

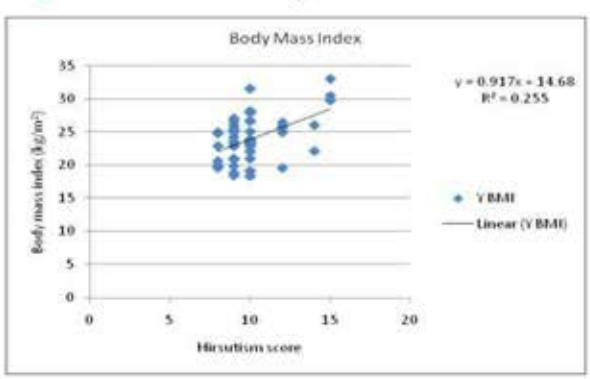

Fig-2: Correlation of body mass index with mild hirsutism.

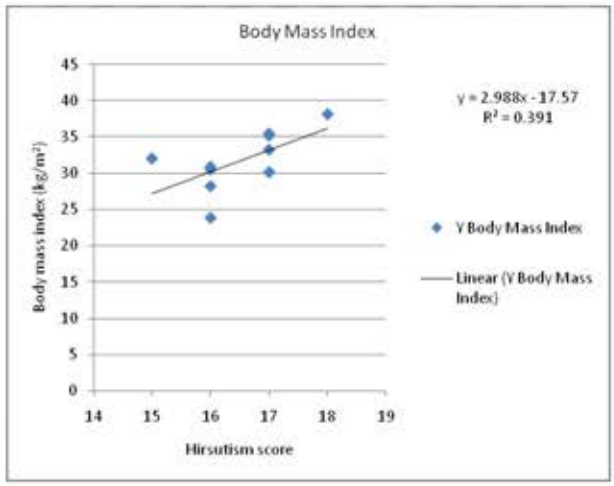

Fig-3: Correlation of body mass index with moderate hirsutism.

Discussion

Hirsutism has a strong, unpleasant impact on the health-related quality of women. It is also more common in women with simple obesity. The relation between obesity and hirsutism may be modified by racial and ethnic characteristics of different populations.[8]

In the present study, the anthropometric characteristics of a group of women with hirsutism and a group of age-matched healthy women was compared. The mean SD waist circumference, weight and BMI values in hirsutes were significantly higher than those in controls. However the differences of height between two groups was not significant ($p>0.05$). These results are comparable with results of a study about the relationship of mean weight, body mass index and waist hip ratio with hirsutism in Iran.[9]

Similarly a clinic-investigative study in India found association of hirsutism with obesity.[10] Another study exhibited that hirsutism was more frequentin patients with high BMI.[11] Schmidt *et al* also concluded that the presence of hirsutism was associated with increased body mass index [12].In a prospective cohort study, Ollila*et al* found that hirsutism is associated with significantly increased weight gain, especially in early adulthood.[13]

In our study, hirsute subjects were divided into mild and moderate groups on the basis of their modified Ferriman-Gallwey scores. On the basis of BMI, majority of normal and overweight subjects (85%) had mild hirsutism while 15% obese subjects had moderate hirsutism. We found that body weight and body mass index were significantly and positively correlated with subjects having mild hirsutism.

Howeverin subjects
having moderate hirsutism, a significant and positive correlation was seen only with body mass index.

In another study, significant correlation was found between score of hirsutism and BMI of the patients.[14] However, Rehman*et al* reported that the correlation of menstrual irregularity, BMI and severity of hirsutism with its cause was found to be statistically not significant but in this study, the relationship of BMI with hirsutism severity was not focused upon.[15] In an another study carried out in black and white population, the overall mF-G score was found to be not affected by age, BMI, the presence of hormonal therapy, oligomenorrhea, or menopause.[16]

An explanation for the differences between the results of these studies is that these studies tended to include greater numbers of older and menopausal women, which may have accentuated the changes in hair growth occurring with age. In view of the findings of previous studies, the results of our study point towards a more investigative role of increased body weight in subjects with low hirsutism scores.

Conclusion

We conclude that the excess terminal hair growth is more common in overweight women having less hirsutism score.

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Original Article

Long Period Vs Short Period Drain Placement in Incisional Hernia Repair

Javaid-ur-Rehman, Saleem Arif and Yasoob Ali

Objectives: To assess the benefit of the long period drain placement after incisional Hernia repair and abdominoplasty for reducing the seroma complications.

Methods: A total of 100 patients were included in this study which had been performed at services institute of medical sciences Lahore between January 2013 to December 2014. In these patients mesh repair of incisional hernia and abdominoplasty had been performed for their incisional Hernia and hanging abdomen. These patient had been divided into two groups, group (1) include 50 patients in which the drain had been left for 3 to 4 days, group(2) include 50 patients in which the drain had been left for 7 to 15 days.

Results: We found that in the group (1), 20 (40%) patients had develop seroma collections and 8 (21.33%) patients had developed wound infection with this seroma and 5 (13.33%) patients developed hematoma collections.

In group (2) we found that only 3 (9.33%) patients developed seroma collection and 1 (4%) patients developed wound infection with this seroma.

Conclusion: There was significant difference in the incidence of seroma formation or surgical wound infection between the two groups. So we can place drain for long period to prevent seroma formation.

Keywords: Incisional Hernia, drain, mesh repair, abdominoplasty.

Introduction

Hernia is a mechanical defect in the abdominal wall and repair of hernia is one of the commonest procedures performed by general surgeons. Repair of incisional hernia is complex due to recurrent operations and infections. Wound-related complications are common after incisional hernia repair with abnormal fluid collections, seroma being the most frequent problem. The use of mesh increases the risk of seroma formation.[1,2] The surgeon's choice of mesh and the position of incorporation are critical in reducing the incidence of postoperative seroma by affecting the tissue plane dissection, closure, and subsequent healing process.[3,4] Most seromas are not clinically relevant because they are asymptomatic and resolve within weeks with expectant management. On the other hand, seromas can become infected and predispose to various wound complications. In many cases of persistent or complicated seromas, fluid aspiration fails to provide final resolution of the collection. Furthermore, fluid aspiration carries the risk of introducing infection, which can be detrimental following mesh placement. The mesh onlay technique, which requires more extensive dissection, is associated with an even greater incidence of seroma formation.

Methods

This is a prospective study conducted at services institute of medical sciences Lahore from January 2013 to December 2014. In this 100 patients were included in which mesh repair of incisional hernia and abdominoplasty was done. We divided the patients into two groups, 50 patients in each groups. All the patients had large incisional hernias due to previous operations and they had given the consent for mesh repair of hernia and abdominoplasty. Unwilling patients, morbid obese patients and high risk patients are excluded from the study. All the patients were operated as lower transverse skin crease incision was made, flaps were raised sac was identified contents were reduced repair of hernia and onlay/sublay mesh applied. Then flaps were cut and wound closed over a two drains. In this we used two drains 18french redivac drains one on each side of the abdomen under the flaps and over the mesh. In group one we removed the drain after 3 to 4 days and in group 2 we removed the drain after 7 to 15 days. These drains were removed when seroma was less 20ml in last 24 hours. The statistics were assessed with spss software version 20.

Results

The demographics were same in both groups with

median age was (39.16 ± 8.9 years). After reviewing the patients we come to know that most common cause of incisional hernias in females were after lower segment caesarian sections, other gynecological surgeries and recurrent Para umbilical hernias. In males the most common cause of incisional hernias was laprotomy, recurrent Para umbilical hernia and sites of stoma. In group 1 seroma occur in 20 patients and haematoma occur in 5 patients and infection occurs in 8 patients. In group 2 seroma occur in 2 patients and haematoma and infection occur in one patient and it is statistically significant.

Table-1: Causes of incisional hernia.

Types of Surgery	Types of surgery	Percentage
Cesarean Sections	21	21%
Hysterectomy	12	12%
Laprotomies	24	24%
Stoma sites	04	04%
Appendisectomies	03	03%
Hernias	36	36%

Table-2: Complications

Groups	Seroma formation	Wound Infection	Haematoma
Group I	20/50	8/20	5/20
Groups II	2/50	0	½

Discussion

Incisional hernia is a frequent complication of abdominal surgery and such hernias causes serious morbidity such as incarceration and strangulation. There are different types of repair of incisional hernias and wound-related complications are common after incisional hernia repair with abnormal fluid collections and infection being the most frequent problems. When mesh is used for repair of larger and more complex incisional hernias, the risk of seroma formation increases. The mesh onlay technique, which requires more extensive dissection, is associated with an even greater incidence of seroma formation. Previously reported rates of seroma occurrence with different types of mesh range from 4% to 8% with polypropylene (Prolene, Marlex) grafts and 5% to 15%with PTFE (Gore-Tex) grafts.[2-6] In most instances, these seromas resolve either spontaneously or with the insertion of drains or serial percutaneous aspirations.[7-9]

In this study we also selected complex incisional hernias in which repair of incisional hernias and abdominoplasty were also done due to obesity and hanging abdominal wall. Most of our surgeons place drains for short period for 3 to 4 days but I usually place drain for 7 to 15 days. So we come to know that if we place drain for short period there are more chances of seroma formation and more chances of infections and if we place drain for more period then there are less chances of seroma formation and wound infection. There are different types of repairs of incisional hernia, suture repair, component separation and mesh repair. Mesh can be applied in different ways inlay, sublay and onlay techniques.[10-13] In suture repair there are more chances of recurrences but fewer chances of infection but in mesh repair there are less chances of reoccurrence but there are more chances of infection due to foreign body reaction. Due to this foreign body reaction there is more tissue reaction which leads to more reactionary fluid production and this fluid needs drainage and in study we place drain for long period for drainage of exudative serous fluid. We observe if we remove drain earlier then this fluid will accumulate under the flaps and later on this fluid become infected leading to delayed recovery. In this study we performed abdominoplasty along with hernia repair in obese patients and in these patients there are more chances of seroma formation although seroma again occurred in 2 patients after long period drain placements which was treated with multiple aspirations or again placement of drain in seroma cavity.

From our study we found that there is statistically significant ($p < 0.5$) difference between the complications that happen when the drain is removed early and there is less complications if it is kept for long period. The evacuation of either hematoma & seroma with tight dressing is an important factor to prevent infection and abscess formation which leads to toxicity and weakening of the repair that may be as a predisposing factor for wound dehiscence or late recurrence. Although long term drain placement also increases chances of infection but dressing under aseptic condition reduces this chances of infection.

Conclusion

There was significant difference in the incidence of seroma formation or surgical wound infection between the two groups.

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CORRIGENDUM

Esculapio
Journal of Services Institute of Medical Sciences Lahore
Volume 12, Issue 03, July to September 2016

In an Original Article,
"Mutational Analysis of HCV Gene Encoding E1 Glycoprotein"
By Muhammad Saad Janjua, Rehman Shahzad, Ghazala Jaffery, Faria Malik , Aneeq Waqar and Hina Bukhari was printed Department of Biochemistry on page # 114. The correct department is Department of Pathology.

Now **Volume 12, Issue 03, July to September 2016** page # 114. Should be read as follow:
Department of Pathology. SIMS/Service Hospital Lahore.

Original Article

Pattern of Dyslipidemia and Other Risk Factors for Coronary Artery Disease and Macrovascular Complications in Diabetic Patients

Muti ullah Khan, Muhammad Latif and Azhar Hussain

Objective: To determine the pattern of dyslipidemia and other risk factors and their association with macrovascular complications in our diabetic patients presenting to OPD (outpatients department) on routine follow up.

Methods: This study was done in medical outpatients department, Akhter Saeed teaching hospital, from December 2014 to August 2015. one hundred diabetic patients, male and female, coming for routine follow up were screened for macrovascular complications, and risk factors like obesity, hypertension, deranged glucose levels and lipid abnormalities were measured and analyzed.

Results: Of the one hundred patients recruited for this study, fifty three were females and forty seven were males. Male patients were more likely to be obese and overweight [5 (10%) and 11 (23%) respectively] than the females [2 (3%) and 10 (19%) respectively]. Males were also more likely to be hypertensive [24 (51%)] than females [23 (43%)]. The average BP (blood pressure) for males was (141±44 SD)/ (91±14 SD) mmHg, and (129±41 SD)/ (85±15 SD) mmHg for females. All the patients had fasting hyperglycemia, however females were having more deranged values [FBS (141±79 SD) mg/ dl for males and (151±91 SD) mg/ dl for females]. Male patients were found to have dyslipidemia predominantly in the form of high total and LDL cholesterol or low HDL cholesterol, while more of the females had hypertriglyceridemia. In this study, high LDL cholesterol or total cholesterol and low HDL cholesterol were found to be associated with hypertension and macrovascular complications. Of the 72 among all the 100 patients with evidence of macrovascular complications, high total cholesterol was seen in 58 (80%) patients while it was seen in 17 (61%) of the remaining patients. High BMI (Body Mass Index) was also independent risk factor for hypertension and coronary artery disease in age matched patients. Increased triglyceride levels did not show any clear correlation with macrovascular complications.

Conclusion: This study shows increased incidence of lipid abnormalities and other risk factors in diabetics especially in patients with evidence of macrovascular disease.

Keywords: Diabetes mellitus, dyslipidemia, macrovascular complications.

Introduction

Diabetes mellitus is a major health problem worldwide.[1] Among the most important complications of disease are the macrovascular complications leading to coronary artery disease (CAD), stroke and peripheral vascular disease and diabetic dyslipidaemia is believed to be a major cause of increased risk of such complications.[2] Patients with type 2 diabetes mellitus have a twofold to threefold increased incidence of diseases related to atheroma[3], the pathological mechanism for macrovascular complications. Thus lipid abnormalities, commonly seen in diabetic patients are major modifiable risk factor for these macrovascular complications and a potential target of preventive treatment. While several international studies have been conducted to prove the correlation between diabetes and dyslipidemia and between dyslipidemia and macrovascular complications, few if any such studies are available for Pakistan. Thus the purpose of current study was to identify the pattern of dyslipidemia and other risk factors, and their association with macrovascular disease in our diabetic patients coming to the OPD for routine visits.

Methods

iThe study was conducted at Akhter Saeed teaching hospital Lahore during the period of August 2014 to June 2015. A total of 100 patients known with type 2 diabetes between the ages of 30 and 60 years coming to outpatients department for routine visits were selected for the study. Informed consent was taken for all the patients.

Detailed physical examination was performed. Blood pressure was recorded with patients in resting state for at least ten minutes. Anthropometric measurements including height and weight were taken and BMI was calculated. Evidence of macrovascular complications was sought by examination of peripheral pulses, neurological examination and by history or ECG evidence of coronary artery disease. Blood samples were taken after at least 8 hours of fasting and sent for routine blood counts, glucose, renal profile, liver function tests, plasma lipids total cholesterol (TC), low density cholesterol (LDL-C), high density cholesterol (HDL-C), and triglycerides (TG). Patients with recent myocardial infarction (MI), renal failure, hepatic dysfunction and other causes of dyslipidemia like nephrotic syndrome or hypothyroidism were excluded from the study.

Results

Of the one hundred patients recruited for this study, fifty three were females and forty seven were males. Male patients were more likely to be obese and overweight [5 (10%) and 11 (23%) respectively] than the females [2 (3%) and 10 (19%) respectively]. Males were also more likely to be hypertensive [24 (51%)] than females [23 (43%)]. The average BP for males was 141 (±44 SD)/ 91 (±14 SD) mmHg, and 129 (±41 SD)/ 85 (±15 SD) mmHg for females. All the patients in the study were found to have fasting hyperglycemia, however females were having more deranged values [FBS 141 (±79 SD) mg/ dl for males and 151 (±91 SD) mg/ dl for females] (table i). Male patients were found to have dyslipidemia predominantly in the form of high total and LDL cholesterol or low HDL cholesterol, while more of the females had hypertriglyceridemia.

In this study, high LDL cholesterol or total cholesterol and low HDL cholesterol were found to be associated with hypertension and macrovascular complications. Of the 72 among all the 100 patients with evidence of macrovascular complications, high total cholesterol was seen in 58 (80%) patients while it was seen in 17 (61%) of the remaining patients (table ii). High BMI was also independent risk factor for hypertension and coronary artery disease in age matched patients. Increased triglyceride levels did not show any clear correlation with macrovascular complications. The number of patients was too small for calculation of individual risk factors separately in male and female patients.

Table-1: Baseline patient characteristics.

Paramters	Obesity			BP	TL	Chol. Mg/dl(±SD)			Fating Glucose
	Ave. BMI (kg/m2.)	Overweight No. (%)	Obese No.(%)	sys/ dias ave (±SD)		LDL-C	HDL-C	Trig.Mg/dl	
Male	24	11(23)	5 (10)	141(±44) / 19 (±14)	207(±21)	140 (±17)	37(±4)	171 (±39)	141 (±79)
Female		10 (19)	2 (3)	129(±41) / 85 (±15)	201(±17)	133 (±16)	36(±5)	176(±42)	151 (±91)

Table-2: Prevalence of macrovascular complications. CAD; coronary artery disease, PVD; .

Type of complications	Number of Patients (%)		
	Males	Females	Total
Any type of macrovascular complication	37 (78)	35 (66)	72 (10)
CAD	16 (34)	16 (30)	32 (32)
PVD	23 (49)	26 (49)	49 (49)
Stroke	3 (6)	10 (2)	4 (4)

Discussion

Diabetes mellitus is a major health problem. In the second half of the 20th century it became obvious that a relentless increase in Type 2 diabetes mellitus (T2DM), affecting the economically affluent countries, is gradually afflicting also the developing world, and hence has been labeled a global pandemic. Based on current trends, the International Diabetes Federation projects that 438 million individuals will have diabetes by the year 2030.[4] WHO ranks Pakistan 7th on diabetic prevalence list.[5] This metabolic disorder causes marked increase in mortality and morbidity compared to non-diabetic person. Those with type 2 diabetes who present in their 40s and 50s have a twofold increased total mortality.[6] The majority of diabetic patients have type 2 diabetes (about 90%) which is frequently associated with insulin resistance, hypertension and lipid disorders. Obesity is a major

environmental factor predisposing to type2 diabetes. Among the major complications of the disease are the macrovascular complications leading tocoronaryartery disease (CAD), stroke and peripheral vascular disease. Dyslipidaemia, frequently associated with diabetes is believed to be a major cause of increased risk of such complications.[7,8] Patients with type 2 diabetes mellitus have a twofold to threefold increased incidence of such complications.

Severalstudies have been conducted for determining the pattern of dyslipidemia and risk of macrovascular complications in diabetic patients, with variable results. These variations probably reflect regional variations or different parameters selected in each study. Despite these differences in the results, almost all studies show clear association of diabetes with abnormal lipid profiles and the presence of macrovascular complications compared with the non-diabetic population. While abundant data is available on this topic from other countries like UK (Turner et al2)and India (Khadke et al4), little is available for our country. We could find only one such study about the pattern of dyslipidemia in diabetic patients and their association with macrovascular complications.

Turner et al[2] report from UKPDS 23 (United Kingdom Prospective Diabetes Study), that increased total and LDL cholesterol as well as low HDL cholesterol was associated with increased risk for CAD in patients with type-II diabetes, even more than that for general population. They did not find any clear association of raised triglyceride levels with cardiovascular events. This is in accordance with our Study. However in contrast to our study, they did not find increased BMI or other measures of obesity to be associated with increased risk. The incidence of overweight and obesity was found to be high in our patients and it was also found to be an independent risk factor for hypertension and CAD, but not by turner et al.[2] Although obesity is a risk factor for coronary artery disease and hypertension in non-diabetic patients[14], it is also a risk factor for diabetes, and once diabetes develops it was not found to be significant risk factor of CAD in other studies. Hypertension is an extremely common comorbidity of diabetes affecting 40-60% of people with diabetes,[9] almost twice as frequently in diabetic as in non-diabetic persons.[13] Hypertension is also a major risk factor for cardiovascular events, such as myocardial infarction and stroke as well as for microvascular complications such as retinopathy and nephropathy.[12] Our study also shows similar results. We found 24 of the 47 male (51%) and 23 of 53 female (43%) patients to be hypertensive. Khadkeet al[4] show increased prevalence of lipid abnormalities in diabetic patients compared to normal population. Another study conducted in Pakistan also showed clearly increased incidence of dyslipidemia in diabetic patients compared with normal controls.[9] Other studies show clustering of several cardiovascular risk factors including obesity, hypertension and dyslipidemia in type 2 diabetic patients.[10]

In one similar study conducted in Pakistan, Alamgiret al[11] showed association of various lipid abnormalities with poor glycemic control in diabetic patients. They also found that high total and LDL cholesterol as well as low HDL cholesterol were associated with macrovascular complication including CAD, stroke and peripheral vascular disease. However, in their study, CAD and stroke was more common type of macrovascular disease than peripheral vascular disease. While in our study, it can be appreciated that patients presented with peripheral vascular disease as the most predominant form of the macrovascular disease. Another study conducted in Karachi also showed similar results, but that was an observational study with much emphasis on clinical manifestations of complications depending upon history only and without in-depth evaluation of patients or critical analysis of results Khuwajaet al.[16]

Ever since the Framingham heart study identified the important risk factors associated with CAD,[15] there has been a great stress to reduce the burden of CVD (Cardio Vascular Disease) by modifying these risk factors.[17] Several of these risk factors are associated with diabetes and their risk is increased several times when associated with diabetes mellitus. Thus identifying these risk factors in diabetics and timely intervention can prevent significant number of coronary events in these patients.[18]

Conclusion

This study shows increased incidence of lipid abnormalities and other risk factors in diabetics especially in patients with evidence of macrovascular disease. Hence routine screening and timely treatment for these risk factors can prevent burden of macrovascular complications.

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Original Article

Depression in Post-Mastectomy Breast Cancer Patients

Shahid Hameed Warris,Sumira Qambar Bokhari,Muhammmad Nasar Sayeed Khan and Nauman Mazhar

Objective: To compare the frequency and association of depression in post-mastectomy breast cancer patients.

Methods: Two Fifty consecutive outdoor breast cancer patients were included in the study that had undergone mastectomy in the preceding 2-4weeks. They were compared with physically healthy matched females who were accompanying the patients suffering from various cancers to the out patient department of oncology units. A semi structured interview and Present State Examination (PSE) were administered to assess symptomatology. Patients were diagnosed as suffering from depression on the basis of Diagnostic and Statistical Manual of Mental disorders; fourth edition (DSM-|V). The Hamilton Rating Scale for Depression (HRDS) was administered to the positive cases in order to determine the severity of the depressive symptoms.

Results: Depressive disorder was found in 20% of post mastectomy breast cancer patients in comparison to 16 % of control group. Depressive disorder was more prevalent (88.8%) in breast cancer females who were younger than their husbands by 0-4 years and those women who had nuclear family system. Among the control group (caregivers/ attendants), depressive disorder was more prevalent (87%) among mothers and sisters of cancer patients (p<O.05).

Conclusion: The patients who are suffering from breast cancer should bescreened for depressive disorder and intervention must be given wherever possible, Moreover care givers /attendants of patients suffering from various cancers and other life threatening illnesses should also be assessed and managed for depressive disorder as a part of multi modal management plan to improve the level of care giving behavior.

Keywords: Breast cancer, depression, post-mastectomy, care givers.

Introduction

Worldwide more than half a million new cases of breast cancer are reported each year.[1] In Pakistan breast cancer was reported to be the commonest malignancy in women and comprises more than 24% of all female cancers.[2] Medical literature suggests that genetic, endocrine and environmental factors may be involved in the initiation and promotion of breast cancer.[1,3,4,5]

Females with breast cancer most commonly present with lump in their breasts[6] Other presenting complaints may be nipple discharge, ulceration and symptoms suggestive of meta stases to other organs.[6,7] A multi disciplinary team consisting of surgeon, radiologist and pathologist perform assessment of the women with suspected breast cancer.[8] Breast cancer is treated by radiotherapy, chemotherapy and hormonal therapy.[9]

Numerous studies have reported psychiatric disturbances in women with breast cancer. Hugh son et al found that one month after mastectomy, more than one third of patients reported depression, anxiety or social dysfunctions and more than half of the patients complained of lethargy or inability to work.[10] Othercommon psychiatric manifestations reported are somatization, hostility, sexual dysfunctions, problems with body image and disturbances in sleep and eatin.[11,12] In a retrospective study, Fallow field et at examined 101 early breast cancer patients after a mean interval of 16.7 months of surgery. Of these, 53 patients were treated with mastectomy. These patients were administrated Patient State Examination (PSE) followed by Diagnostic and Statistical Manual of Mental Disorders; third edition (DSM-lll) criteria for mood disturbance. 2l% of these patients were identified as suffering from depressive disordered.[13] In a prospective study, same authors examined 154 mastectomy patients along with lumpectomy patients with stage I and ll breast cancer. In this study serial assessments were made in which PSE was administered along with Hospital Anxiety and Depression Scale (HADS), Rotterdam Symptoms Check List (RSCL) and Spielberger State Trait Anxiety

Inventory. After mastectomy at two weeks, 3months and it 12 months, frequency of depression was 29%,27% and 21%respectively.[14] Aragona et al.reported major depression in only 2% of un-treatedearly 149 breast cancer patients prior to any surgical intervention. They used the instruments similar to the present study.[15] By using HADS, Pinder et al found12% of admitted patients with long history of advanced inoperable breast cancer recorded high score on depression.[16] Izhar el al reported that more than 80% of admitted female cancer patients had a score above the cut-off point on depression sub-scale of HADS.[17] In an another study, Haider diagnosed depression of moderate to severe intensity in 90% of indoor cancer patients as compared to 67% of control group suffering from other physical diseases. Females with breast cancer reported the highest mean depression scores as compared to the patients having cancer in other parts of the body.[18] It was summarized by Aragona et al that depression constituted a part of natural history of breast cancer as it occurred even before the awareness of the diagnosis.[15]

Diagnosis of psychiatric illnesses in breast cancer patients showed a very low concordance rate of only 23% between the oncologists and psychiatrists. It was concluded by Pendlebury et al that the oncologists frequently under-diagnosedand under-estimated the frequency and severity of depression in breast cancer women.[19] It was commented in many studies that depression and psychiatric morbidity in breast cancer patients was mostly associated with factors like age, marital status, personality, coping style, social class, performance status, physical complaints, experiencing of stressful conditions in the past, emotional and social support system, giving information about the disease and its treatment etc.[11,20,21,22,23]

In care givers of cancer patients the psychiatric disturbances are reported to be17%-33%.[24,25,26] Kurtz et at reported in their study that younger the age of cancer patients more the care givers tended to be depressed.[27] Other studies showed that the presence of pain, sleep impairment, other physical symptoms, limitations of activity of daily living, lower income, living only with the patients associated with high level of anxiety and depression in the care givers.[25,26,28,29,30,31,32,33,34]

Mastectomy in patients with breast cancer can severely affect their body esteem. It also changes the emotions and attitudes of patients toward their body and causes psychological reactions such as depression, anxiety, and stress.[35] The present study is being undertaken to highlight the frequency of depressive disorder in post-mastectomy breast cancer patients in Pakistani setting, which should help to develop better awareness of this frequently neglected complication of breast cancer.

Methods

This was a hospital based case control study which was conducted in the Department of Radiotherapy and Oncology, Mayo Hospital and the Institute of Nuclear Medicine and Oncology (INMOL), Lahore from August 2002 to April2003. 50 consecutive outdoor post mastectomy breast cancer patients, with the age range of 30 years and above, before the administration of radiotherapy and chemotherapy were allocated to group A and 50 female attendants of various cancer patients attending the outdoor, matched with age and socio-economic status were included in group B, which is a control group. Subjects suffering from physical illnesses and those who had past psychiatric illnesses were excluded from both the groups. In addition to these, patients suffering from non-malignant diseases of breast and those breast cancer patients who were treated by methods other than mastectomy were also excluded from group A. Patients of both groups were given semi-structured psychiatric interview employing Urdu version of Present State Examination (PSE) (Wing et al 1974).[36] Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)[37] was used for the diagnosis of depression and Hamilton Rating Scale for Depression (HRSD) (Himilton 1967)[38] was administered to positive cases to measure the severity of depressive symptoms. PSE covers the patient's symptoms during the previous four weeks. It consists of 140 items and each symptom is rated on 3-4 point scale. Its inter-rater reliability for symptoms is+0.77. HRSD is rated on either 5-point scale or 3-point scale, its inter-rater reliability is +0.90 with a correlation of 0.96.

Hospital record of each study group patient was examined and brief history from woman of both groups was obtained. Written informed consent was obtained from the subjects of both groups. The collected data was entered on SPSS Version 11 for analysis. Simple descriptive statistics was used to analyze the demographic variables (age and socioeconomic status). Frequency and percentage of depression and its severity was calculated in both groups. For the comparison of the two groups regarding the severity of depression-test was used. A p-value of equal to or less than 0.05 was considered as significant.

Results

Mean age of patients of group A was 48.16 years, SD 10.824 with age range being 35-70 years. Mean age of the subjects of group B was 48.18 years, SD10.817 with the age range of 35-70 years.

Out of 50 patients, 10(20%) patients of group A were diagnosed to be suffering from depressive disorder, whereas of group B, 8 (16%) subjects were also found to be depressed ($Z=0.52; p>0.05$). Out of the 10 depressed patients of group A, 8patients secured a score of 14 or above on HRSD.[38] Severity of depression among these patients was moderate or severe. In comparison, 3 subjects of group B scored in the range of moderate of severe depression. This difference was statistically significant ($Z=1.84$; $p<0.05$). This means that higher proportion of breast cancer patients suffered with more severe depression as compared to the attendants. Among the breast cancer females, depressive disorder was significantly associated with small age difference (0-4 years) with their husbands and with nuclear family system. **(Table1,2)** Depressive disorder was significantly more prevalent in women of both groups who were house wives, belonging to lowest category of income, got married at an age younger than 30 years and those women who had children five or less in number. Depressive disorder was unrelated to age, place of residence, marital status and education of the cases and controls. Of the total of 8 depressed subjects of group B,4 (50%) attendants were accompanying their adult daughters with cancer,3 (37.5%) depressed attendants were accompanying their sisters with cancer and one depressed attendant was accompanying her young son with cancer. These figures reveal that depression was more common among those female attendants or care givers who were accompanying their daughters or sisters suffering with various cancers. **(Table3)**

Table-1: Distribution of age difference with husband.

Age Difference (Years)	Group A* (N=48)			Group B* (N=48)		
	Depressed No%	Non- Depresses No%	Total No. Patients No%	Depressed No. %	Non- Depresses No. %	Total No. Patients No.%
0-4	8 (88.8)**	18 (46.1)	26 (54.1)	2 (28.5)**	19 (46.3)	21 (43.7)
5-9	0 (0)	11 (28.2)	11 (22.9)	2 (28.5)	11 (26.8)	13 (27.0)
10-14	0 (0)	6 (15.3)	6 (12.5)	3 (42.8)	10 (24.3)	13 (27.0)
15-19	1 (11.1)	2 (5.1)	3(6.2)	0 (0)	0 (0)	0 (0)
>20	0 (0)	2 (5.1)	2 (4.1)	0 (0)	1 (2.4)	1 (2.0)
Total	9	39	48	7	41	18

** = Out of groups A & B, 2 were unmarried in each group / ** = P<0.05*

Table-2: Distribution of family system.

Age Family System	Group A* (N=48)			Group B* (N=48)		
	Depressed No%	Non- Depresses No%	Total No. Patients No%	Depressed No. %	Non- Depresses No. %	Total No. Patients No.%
Nuclear	9 (90)**	28 (70)	37(74)	4(50)	24(57.1)	28(56)
Estended	1 (10)	12 (30)	13 (26)	4(50)	18(42.8)	22(44)
Total	10	40	50	8	42	50

** = Out of groups A & B, 2 were unmarried in each group / ** = P<0.05*

Table-1: Distribution of depression in attendants according to the nature of their relationship with the patients

Attendant- Patient Relationship		Group B Subjects (N=50)		
Attendants	Patients	Depressed No. %	Non- Depresses No%	Total No. Patients No%
Mother	Daughter	4(50)	3(7.1)	7(14)
Mother	Son	1(12.5)	3(7.1)	4(8)
Daughter	Mother	0(0)	4.(9.5)	4(8)
Daughter	Father	0(0)	0(0)	0(0)
Sister*	Sister	3.(37.5)	15(35.7)	18(36)
Sister	Brother	0(0)	1(2.3)	1(2)
Attendant	Cousion	0(0)	4.(9.5)	4(8)
Attemdant	Relatives	0(0)	12(28.5)	12(24)
Total		8	42	50

Discussion

Findings of present study are closer to study conducted by Fallow field et al who reported depressive disorder in 21% of post-mastectomy patients but differs from present study in the way that it was a retrospective study and assessment was made after a mean interval of 16.7 months after surgery. [13] The prospective study by Fallow field differs from the present study in the sense that in it multiple serial assessments were made, sample size was quite large and three types of self-rating instruments were used.[14]

The diagnosing of major depression in only 20% of breast cancer patients in Aragona's study may be attributed to the fact that his patients remained untreated and had to undergo the distress of surgery and loss of a body part.[15]

Pinder's study differs from the present study in the way that it assessed the patients with long history of advanced inoperable stage of disease, many patients were admitted, and different type of instrument used. Unexpectedly, the researchers diagnosed depression in only 12% of patients, which might be a result of adjustment in these women because of long history of the disease.[16]

With reference to severity of depression, the finding of this study is very close to that of the study conducted by Haider, who reported moderate and severe depression in 90% of cancer patients. This study differs from the present study in respect that the patients were in the advanced stage of cancer, these patients were admitted in the oncology department and were receiving che motherapy, and 314 of the patients were those who were suffering from cancers other than breast malignancy.[18]The present study shows clearly that more than 4/5 of depressed breast cancer patients were younger than their husbands by 0-4 years as compared to little more than 1/4 of depressed care givers of various cancer patients. This finding can possibly be explained by the fact that in our society smaller age difference with husbands causes the natural difference of opinion between the couples to come to surface more readily. This causes more conflicts and stressful relationship with husbands. Such stressful interpersonal relationships with their husbands in the past are more likely to develop depression when they are faced with new difficult situation like breast cancer, though this explanation is in conformity with the study by Maunsell at al [21], it needs further work to reach to conclusion. This study also shows that majority of depressed breast cancer patients had nuclear family system as compared to depressed attendants of control group. The plausible explanation of this finding could be that in nuclear family system there is lack of adequate social and emotional support from the parents and siblings of breast cancer patients. This explanation is supported by other studies.[22,23]

The present study also highlights the frequency of depressive disorders in care givers of the patients suffering from various cancer was nearly equal to the frequency of depressive disorder in breast cancer patients, though in majority of these attendants the severity of depressive symptoms was mild. This finding is in conformity to many studies.[24,25,26]

Conclusion

The present study shows that 2 to 4 weeks after mastectomy one out of five breast cancer patients were suffering from depressive disorder in comparison to one out of six attendants of patients suffering from various cancers.The present study suggest that when the physicians and surgeons assess the breast cancer patients they must keep the smaller age differences of these patients with their husbands and nuclear family system in mind as these two factors may predict higher prevalence of depression in this population. It is also suggested that along with cancer patients the attendants /care givers must be assessed for depression. Due to mild severity of depression in care givers it is quite easy to treat them that may improve the level of their care giving behavior.

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Original Article

Comparison of Expulsion Rate In Immediate Versus Delaye Insertion of Intrauterine Device in Females Presenting After Delivery

Huma Arshad, Faiqa Saleem, Muhammad Shahid and Muhammad Tayyab

Objective: To compare the frequency of expulsion in immediate versus delayed insertion of intrauterine device in females presenting after delivery

Methods: This present randomized control trial was conducted at Department of Obstetrics and Gynecology, Jinnah Hospital / AIMC, Lahore. Non-probability purposive sampling technique was used in this study. Informed consent was taken from all 200 patients. Demographic information (name, age, BMI and contact) were recorded. Females were divided in two groups on the basis of time of device insertion i.e. immediate or delayed (as per operational definition). Females were followed for 6 months and x-ray was performed to confirm expulsion was labeled. Both groups were compared for IUD expulsion by using chi-square test taking p-value<0.05 as significant. Data was stratified for parity & obesity. Chi-square test was applied post-stratification.

Results: The mean age of the patients was 28.99±6.31 years. The mean BMI of the patients was 27.06±3.83 kg/m2. In our study the IUD expulsion was observed in 15% patients. Statistically there is insignificant difference was found between the study group and IUD expulsion of the patients. i.e p-value=0.23. Only significant difference was found between the study groups with obese patients and IUD expulsion of the patients i.e. p-value=0.02.

Conclusion: The evidence found in our study suggests that both the immediate post-partum insertion of IUDs and delayed insertion of IUDs are safe and effective.

Keywords: IUD Expulsion, parity, postpartum, delivery, delayed insertion, immediate insertion

Introduction

Post-partum time is one of the critical period for newborn and mother and associated with high rates of morbidity and mortality. This is a risky period and also the women are vulnerable to have unintended pregnancy. Studies show that adverse outcomes like abortions, premature labor, PPH, LBW babies, fetal loss and maternal deaths are more in pregnancies taking place within 24 months of a previous birth. An Indian study recommends that contraception must be practiced in this special period because 65% women in the first year post-partum period fulfil this study criteria for family planning.[1] Intrauterine device is inserted on outpatient basis and should be be performed by trained healthcare professionals for this job. Intrauterine device is a popular and successful way of contraception in reversible way.[2] After surgical abortion to reduce the incidence of an unwanted pregnancy, the IUC can be placed immediately after this procedure to avoid undesired future complications. Intrauterine device insertion at this moment is associated with safety and well documented efficacy.[3,4] Expulsion rate was higher as observed after immediate insertion in comparison to delayed insertion.[5] A study reported that rate of expulsion was 24.0% with immediate IUD insertion and 4.4% only with delayed IUD insertion. The difference between both groups was significant (p-value=0.008).(6) But another study has reported that the rate of expulsion was 5.04% with immediate IUD insertion and 2.7% only with delayed IUD insertion. The difference between both groups was insignificant (p-value=0.19).[4] Rationale of this study is to compare the frequency of expulsion in immediate versus delayed insertion of intrauterine device in females presenting after delivery. Literature has reported that immediately IUD insertion is associated with more expulsion rate as compared to delayed IUD insertion but controversial results are also present which showed that whether IUD is inserted immediate post-placental or delayed post-partum, there is no difference for expulsion rate. So to confirm whether expulsion rate is significantly higher with immediately IUD insertion or not, we want to conduct this trial. Through this study we will also get local magnitude which will be helpful in future to predict expulsion rate with immediate IUD insertion as compared to delayed IUD insertion. This will help to improve our practice and local guidelines and to achieve more patients' satisfaction.. These are one form of mostiThe study was conducted at Akhter Saeed teaching hospital Lahore during the period of

most effective type of reversible and long-acting way of contraception which are successful in controlling unwanted births.[7] In the first year of use, Copper IUD is associated with about 0.8% failure rates in comparison with levonorgestrel IUD has a failure rate of about 0.2%.[8] Those who did not carry children before, evidence supports safety andeffectiveness of this procedure and at the same time IUDs do not disturb breastfeeding and can be placed just after delivery.[9] They have a role to be used after an abortion.[10] Once removed, , fertility returns to normal in short period of timeeven after long term use.[11] Copper IUDs sometimes increase menstrual bleeding and cause more painful spasmodic cramps.[12] IUDs with hormonal component may reduce menstrual bleeding or sometime stop menstruation forever.[9] The symptoms of cramping can be addressed with NSAIDs.[13]

Methods

This randomized controlled trial was done at Unit III, Department of Obstetrics and Gynaecology, Jinnah Hospital / AIMC, Lahore.Sample size of 200 cases; 100 in each group is calculated with 80% power of test, 1% level of significance and taking expected percentage of IUD expulsion i.e. 24.0% with immediate IUD insertion and 4.4% with delayed IUD insertion in females presenting after delivery. Sampling Technique was Non-Probability, Purposive Sampling.

Patients of age 20-40years with parity <6, were included, presenting in labour for normal delivery at term and Females with an allergy or other contraindications to use of the levonorgestrel-releasing IUD were excluded from the study.

After obtaining permission from hospital ethical committee, 200 females fulfilling the selection criteria were enrolled in the study from labour room of Department of Obstetrics and Gynaecology, Jinnah hospital, Lahore.Informed consent was taken. Demographic information (name, age, BMI and contact) were recorded. Femaleswere divided in two groups on the basis of time of device insertion i.e. immediate or delayed (as per operational definition). Females were followed for 6 months and x-ray was performed to confirm expulsionwas labelled (as per operational definition). All the data was collected using the proforma.SPSS software (version 21) was used for data analysis. Quantitative data like age and BMI was presented as mean and standard deviation. Qualitative data like parity, IUD expulsion was presented as frequency and percentage. Both groups were compared for IUD expulsion by using chi-square test taking p-value<0.05 as significant. Data was stratified for parity & obesity. Chi-square test was applied post-stratification.

Results

Total 200 female patients were enrolled in this study. The mean age of the patients was 28.99±6.31 years with minimum and maximum ages of 20 & 40 years respectively. In this study 32(16%) patients had parity one, 52(26%) patients had parity two, 53(26.50%) had parity three, 42(21%) had parity our and 21(10.50%) patients had parity five. In this study, IUD expulsion was observed in 15% patients and IUD was observed to be in its original position in 85% patients. **Fig-1**

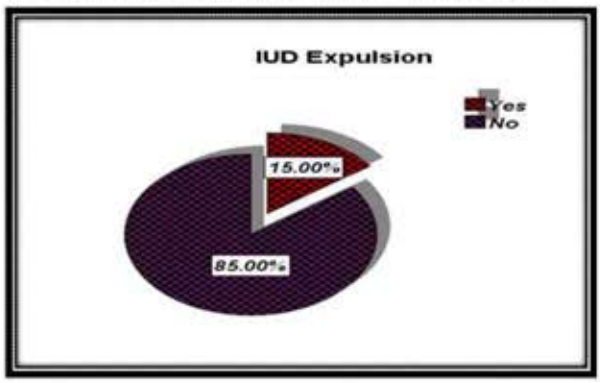

Fig-1: Frequency distribution of IUD expulsion

The study results showed that IUD expulsion was found in 30 patients in which 12 were from delayed group and 18 were from immediate group, similarly IUD expulsion was not observed in 170 cases in which 88 were from delayed group and 82 were from immediate group. Statistically there is insignificant difference was found between the study group and IUD expulsion of the patients i.e. p-value>0.05. **Table-1** In obese case, the IUD expulsion was found in 16 patients in which 5 were from delayed group and 11 were from immediate group. In non-obese cases, the IUD expulsion was found in 14 patients in which 7 were from delayed group and 7 were from immediate group. Statistically there is significant difference was found between the study groups and IUD expulsion whether patients is obese or non-obese i.e. P-value<0.05.**Table-2**

The study results showed that the mean height of the patients was 5.40±0.23 meters with minimum and maximum heights of 5 & 5.80 meters respectively. The mean weight of the patients was 71.53±8.47 kg with minimum and maximum weight of 58 & 88 kg respectively. The mean BMI value of

the patients was 27.06±3.83 kg/m2 with minimum and maximum BMI of 19.40 & 36.60 kg/m2 respectively. **Table-3**

Table-1: Comparison of IUD expulsion in both study groups n=(200)

		Study Groups		
		Delayed	Immediate	Total
IUD Expulsion	Yes	12 (12%)	18 (18%)	30 (15%)
	No	88 (88%)	82 (82%)	170 (85%)
	Total	100(100%)	100 (100%)	200 (100%)

Table-2: Comparison of IUD expulsion in both groups stratified by BMI.

IUD Expulsion		Study Groups		
		Delayed	Immediate	P value
Obese	Yes	5	11	0.02
	No	25	13	
Non-Obese	Yes	7	7	0.026
	No	62	69	

Table-3: Descriptive statistics of Anthropometric measurement of patients n (200)

	n	Height (Meter) 200	Weight (kg) 200	BMI (KG/m²) 200
Anthropometric measurement	Mean	5.40	71.53	27.06
	SD	.23	8.47	3.83
	Minimum	5.00	58.00	19.40
	Maxmium	5.80	88.00	36.60

Discussion

Diabetes This present Randomized Controlled Trial was conducted at Department of Obstetrics and Gynecology, Jinnah Hospital / AIMC, Lahore to determine the frequency of expulsion in delayed versus immediate insertion of intrauterine device in females presenting after delivery.Total 200 female patients were enrolled in this study. The mean age of the patients was 28.99±6.31 years with minimum and maximum ages of 20 & 40 years respectively. Right after child birth, inserting an intrauterine device (IUD) can be safe and good for different reasons. The woman at this time when she is not having pregnancy and may be planning for birth control. The study results showed that IUD expulsion was found in 30 patients in which 12 were from delayed group and 18 were from immediate group, similarly IUD expulsion was not observed in 170 cases in which 88 were from delayed group and 82 were from immediate group.WHO in 1980 compared expulsion and pregnancy rates in this time period and reported them to be excessive.[14]Study from Colombia has reported that 95% of women had a consent for immediate post-partum IUD placement and wished to have it done. Those ladies who wished later insertion, 45% of them ultimately had an IUD placed. Delay in decision especially after discharge from health facility makes it inconvenient and expensive with addition of a return visit.[15] In our study IUD expulsion was observed in 30 (15%) patients. Among these patients expulsion in 12 patients was observed in delayed group and expulsion in 18 patients was observed in immediate group. In obese case, the IUD expulsion was found in 16 patients in which 5 were from delayed group and 11 were from immediate group. According to our study both groups were found insignificant. i.e. p-value=0.23. Some of the studies discussed below according to their findings. The mean BMI value of the patients was 27.06±3.83 kg/m2 with minimum and maximum BMI of 19.40 & 36.60 kg/m2 respectively. Chen 2009 studied delayed versus immediate post-partum insertion of the levonorgestrel-releasing IUD. It was more likely for the immediate group than the delayed insertion to be associated with expulsion by six months (23.5% vs 4.4%) (OR 6.77; 95% CI 1.43 to 32.14). Both groups were comparable in terms of pregnancy (was not found) and in use after six months (84% and 77%, respectively). [16]Celen et al recommended that CuT 380 models is an effective way to achieve objectives in immediate post-placental insertion, it is useful and safe and at the same time it is convenient. This mode is a cost effective procedure for early postpartum contraception. [17] 157 women were randomly selected in a study in Mexico and were followed to receive the CuT380A or the multiload Cu375 either postplacentally [within 10 min of placental delivery (immediate), n=64] or between 10 min and 48 h after delivery (delayed, n=93). At 1 year of follow-up, expulsion rates were 9% and 13% for immediate post placentalinsertion after cesarean and vaginal delivery, respectively, and 4% and 12% for delayed postpartum insertion, respectively (p=.3).[18]1132 Egyptian women were studied in one prospective cohort study after postpartum insertion of a CuT380A IUD over 3 years: 1016 IUD placements occurred within 10 min of placental delivery (immediate) and 116 were inserted between 10 min and 48 h after placental delivery (delayed). Expulsion rates were 2.4 and 2.6 per 100 women years for the immediate and delayed groups, respectively (pN. 05).[19]

Conclusion

The evidence found in our study suggests that both

The immediate post-partum insertion of IUDs and delayed insertion of IUDs are safe and effective. We found that IUD Expulsion was higher for immediate versus delayed insertion with statistically insignificant results.

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Case Report

SHABBIR SYNDROME: A CASE REPORT AND REVIEW OF ITS GENETIC BASIS

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Abstract: Shabbir syndrome is a rare, progressive, multisystem disorder with an autosomal recessive pattern of inheritance. It mainly afflicts children from Punjabi Muslim families of Pakistan and India. The genetic anomaly has been mapped as a mutation in LAMA3 gene on chromosome 18q11.2.

A 17-year-old male presented to us with history of recurrent skin ulcers, nail dystrophy and laryngeal obstruction. Fresh ulcers, older crusted ulcers and cicatrisation in his head and neck area were strikingly obvious. Skin biopsy was submitted and revealed characteristic exuberant granulation tissue with a mixed acute and chronic cell infiltrate. Other features are also described.

LAMA3 gene is responsible for the production of laminin α3 which is one of the three components of laminin, a heterotrimer. Laminin is an important part of the cell membrane and extends into the dermis. Its presence is a signal to the dermis that the basement membrane is intact and the production of granulation tissue is kept in check. Abnormal lamininfails to do it resulting in excessive, undesirable granulation tissue production. Understanding this feedback mechanism may enable us to control the production of granulation tissue in Shabbir syndrome as well as other diseases like rheumatoid arthritis and chronic venous ulcers.

Keywords: Shabbir syndrome, laryngo-onycho-cutaneous syndrome (LOCs), Laryngeal and ocular granulation tissue in children from the Indian subcontinent (LOGIC syndrome), granulation tissue.

Introduction

In 1986, Professor Syed Ghulam Shabbir et al published a series of 22 children from 12 families who had presented with chronic skin ulcers, hoarseness of voice and dystrophic changes in nails. The disorder was named laryngo-onycho-cutaneous syndrome or LOCS but it soon came to be known as Shabbir syndrome.[1] This was soon followed by reports from elsewhere which elaborated further on this strange disorder which consistently seemed to affect children from Muslim families from Punjab province in Pakistan and India. The parents were consanguineous in the vast majority of cases and more than one offspring was seen to be affected frequently. These observations hinted it to be a disease with autosomal recessive inheritance.[2,3] Eyes were described to be another target organ of the disease which showed uncontrolled proliferation of granulation tissue in dermal and submucosal areas.Several patients showed dental abnormalities as well.[4] It was proposed that it should be called LOGIC syndrome, an acronym for Laryngeal and Ocular Granulationtissue in Children from the Indian subcontinent.[2,3,5]

The disease manifested itself in the neonatal period or infancy. It varied in its intensity and was fatal in a large proportion of cases. The major cause of death was laryngeal obstruction followed by infection in skin ulcers. Blindness was also frequently reported.[6] The disease was found to be frustratingly refractory to the treatment modalities available at the time, for example, antibiotics, anti tuberculous drugs, anti leprosy drugs, steroids etc. Intriguing as it is, it remains a rare disease with fewer than 50 cases having been reported so far.[5,7]

A case of Shabbir syndrome was recently encountered and is presented here along with a brief literature review.

Case Report

A 17-year-old male presented to Department of Plastic Surgery,Jinnah Hospital Lahore. He gave history of chronic ulcers all over his body since birth.He also gave history of recurrent respiratory infections, difficulty in speech since childhood. He had an episode of respiratory obstruction one year back which he had been relieved by laser 2 years ago. He gave no family history of similar ailments. He had 3 siblings who were all normal. His parents were first cousins.

He had a hoarse voice. There was widespread ulceration of skin all over his head and neck area. It was more marked on his face where fresh ulcers, older crusted ulcers and cicatrisation were striking **(Fig 1).**

There was pronounced involvement of left lower lid and conjunctiva **(Fig 2).** There was marked nail dystrophy involving both hands (Fig 3). Hair growth was unaffected (Fig 1).Rest of his body was spared though he gave history of occasional ulceration elsewhere **(Table 1).**[8]

Table-1: The major phenotypic manifestations of Shabbir syndrome, their frequency, where determined, and their presence and severity in our patient.[8]

S. No.	Description	Frequency	Whether present in our pt.
1	skin ulcer	Hallmark (90%)	++
2	abnormal pigmentation of the oral mucosa	Hallmark (90%)	+/-
4	abnormality of the toenails	Hallmark (90%)	++
3	opacification of the corneal stroma	Hallmark (90%)	-
5	tracheoesophageal fistula	Hallmark (90%)	-
6	Anonychia	Hallmark (90%)	-
7	abnormality of the voice	Hallmark (90%)	++
8	abnormality of the fingernails	Hallmark (90%)	++
9	abnormality of dental enamel	Hallmark (90%)	++
10	recurrent respiratory infections	Typical (50%)	++
11	respiratory insufficiency	Typical (50%)	++
12	recurrent loss of toenails and fingernails	Not determined	++
13	Hoarse cry	Not determined	+/-
14	Weak cry	Not determined	+/-
15	Amelogensesis imperfecta	Not determined	++
16	Abnormmality of the eye	Not determined	+

The Department of Plastic Surgery planned reconstruction of his left lower lid.

Two of his skin lesions were sampled and submitted to Department of Pathology, Allama Iqbal Medical College, Lahore. Gross examination of these revealed two tiny grey white fragments measuring 0.3x0.2x0.2 cm in aggregate. One of them was partially skin covered. Microscopic examination of biopsy revealed two fragments mostly comprised of granulation tissue **(Fig 4 and 5)**. One of these had a partial covering of epidermis. This showed thinning over most areas and a central area of ulceration **(Fig 4)**. Both fragments contained heavy infiltration by a mixed but mostly chronic inflammatory infiltrate **(Fig 4 and 5).** Overall the findings were quite nonspecific.

Shabbir syndrome is a rare, progressive, multisystem disease with an autosomal recessive pattern of inheritance.[9]There have been steady, incremental advances in our understanding of its genetic basis. Some of these are also shedding light on mechanisms underlying control of granulation tissue formation and the complex interactions between keratinocytes and underlying dermis. The initial grim picture is being replaced by a more optimistic one.

The genetic defect has been localized to a region on chromosome 18q11.2. This region includes the laminin alpha3 (*LAMA3*) gene. The protein coded by this gene is the alpha 3 subunit of laminin 332 (formerly called laminin 5). More specifically, a frameshift mutation coded as 151insG, has been identified. A frameshift mutation is one that involves insertion or deletion, in the DNA sequence, of a group of nucleotides the number of which is not divisible by three. As is well known, nucleotides work in groups of three; each group being called a codon which encodes for one amino acid. The result of such insertion or deletion is that the entire frame of transcription is altered producing proteins grossly divergent from the ones intended. This also affects the "stop codons" and so the resulting protein is either abnormally long or abnormally short. In case of Shabbir syndrome the new protein is shorter by 226 amino acids at its N terminal. This abnormal, truncated protein is obviously unable to perform its required function. LAMA3α is secreted by basal keratinocytes, joins β and γ subunits to form laminin332, and gets incorporated into the basement membrane whereits N terminal negatively regulates granulation tissue formation by the underlying mesenchyme. Its presence signals to the underlying mesenchyme that the basement membrane is intact. Loss of this feedback triggers an unchecked proliferation of granulation tissue which is the hallmark of this disease. This also explains why there is greater proliferation of granulation tissue at sites where there is even mild but repetitive trauma such as the skin, vocal cords, eyes and nails. This theory is called the Keratinocyte-Mesenchymal miscommunication theory.[9,10,11]

Shabbir syndrome shares some features with epidermolysis bullosa and has been classified as a subtype of junctional epidermolysis bullosa.[6,12,13] This implies that these disorders might be amenable to similar modes of treatment.[14] Since its original description it was thought to afflict Punjabi, Muslim families only, but recently cases have been reported from elsewhere like Iran. These cases are clinically indistinguishable from Shabbir syndrome though the genetic anomaly is slightly different.[13,15]

The diagnosis is usually straightforward. A list of

manifestations along with their frequencies has been compiled. Our patient suffered from most of the expected predicaments **(Table 1, Fig 1-3)**.[8]

Fig-1: Photograph of patient, fresh ulcers, crusted ulcers and cicatrisation are strikingly obvious.

Fig-2: There is pronounced involvement of lids and conjunctiva.

Fig-3: There is marked nail dystrophy involving both hands.

Microscopic findings are quite nonspecific and only reveal masses of granulation tissue with acute and chronic inflammatory cells. Similar features were seen in our patient **(Fig 4 and 5)**.[5]

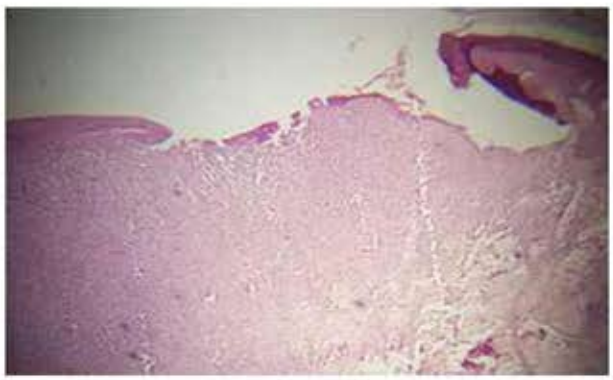

Fig-4: Photomicrograph showing exuberant granulation tissue in the dermis. Epidermis shows thinning and central ulceration. (H & E, x200).

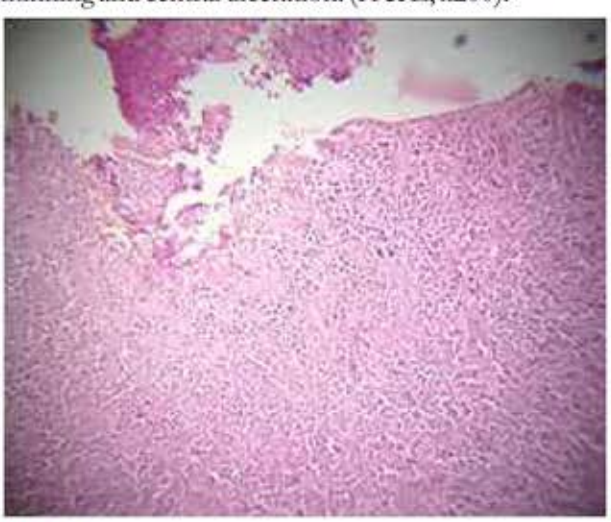

Fig-5: High powered view depicting granulation tissue heavily infiltrated by a mixed acute and chronic inflammatory infiltrate. (H & E, x400).

Numerous drugs with different modes of action have been used with variable success. These include thalidomide, an immunomodulatory drug; cyclosporine, an immunosuppressant; topical 5FU, a cytotoxic agent; and systemic steroids.[10,16]

Laryngeal obstruction is one of the feared complications of Shabbir syndrome and along with skin infections accounts for most of the premature deaths in these patients. Laser therapy has been reported to be partially successful in relieving laryngeal obstruction.[5,14] Our patient was also benefitted from it, and has not had a relapse in two years.

Other, newer methods are being explored to manage the various complications. Dryness of eyes and conjunctival ulcers are major contributors to

blindness. Recent reports describing amniotic membrane transplantation are encouraging. It is supposed to act by providing mechanical protection as well as delivering healthy laminin 332 to the tissues, temporarily compensating for their deficiency of this important factor. Conjunctival and corneal stem cell transplantation is also being considered but would require long term immunosuppression. Buccal and nasal mucus membrane autografts are another option in patients where these are spared of disease.[10] One rather drastic, multistage procedure called osteo-odonto-keratoprosthesis (OOKP), has recently been tried in a patient of Shabbir syndrome. This process is designed to help patients with the most severe corneal and ocular surface problems while the posterior segment is intact. In various steps the front area is debrided and then a new anterior surface built by combing tissues from the patient's tooth, its surrounding bone and buccal mucosa.[7]

Gene replacement therapy is another avenue to be explored. It would involve ex vivo, retroviral transduction of autologous epithelial cells. These could then be reintroduced to effected areas. Another approach being considered is production of recombinant laminin 332. This would involve the insertion, within bacterial plasmids, of DNA sequences responsible for producing laminin 332. As these bacteria divide and multiply, they can be used as factories for the production of this protein. The major impediment to this approach is the large size of laminin 332 which, as already stated, is a heterotrimer. This huge molecule would find it difficult to traverse epithelial layers to reach the basement membrane where its action is required. So the current aim is to produce a smaller recombinant peptide analogue that would replace the 226 amino acid missing portion of laminin3α already discussed. Finally, the ultimate accomplishment would be development of a transgenic mouse model of Shabbir syndrome that would allow testing the efficacy of these methods.[10]

In conclusion, molecular basis of Shabbir syndrome is an area of active study, facts have emerged slowly like peeling away the layers of an onion. The following interesting observations should be taken note of:

a) Determination of the precise gene defect of any inherited disease would be the first step towards its management.[9]
b) Various, apparently dissimilar, diseases may share genetic aberrations making it possible to find common treatment modalities, for example, LAMA3α defects have been described in patients of junctional epidermolysis bullosa, German atopic dermatitis and amyotrophic lateral sclerosis.[12,17]
c) Excessive and undesirable granulation tissue formation is a problem in several more common conditions such as rheumatoid arthritis, chronic venous ulcers, transplant surgery etc. A fuller understanding of the control mechanisms could lead to the identification of novel targets for therapeutic interventions in these conditions as well.[9]
d) Diligent follow up of reported patients has indicated that those who survive into the second decade generally fare better.[11] We hope this will be case in our patient too.

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Answer Picture Quiz

Aberrant right subclavian artery (ARSA)

ARSA is the most common aortic arch anomaly and aneurysmal dilatation of proximal portion of aberrant right subclavian artery is common and referred to as Kommerell diverticulum which appears as bulbous enlargement of proximal subclavian artery at its origin from aortic arch, posterior to oesophagus.

Medical News

NEW STATIN GUIDELINES ISSUED FOR PRIMARY CVD PREVENTION

Statins are a class of drugs commonly used to treat a variety of heart-related problems. However, statins can also be used preventively. The United States Preventive Services Task Force have issued new recommendations regarding the use of statins for prevention of cardiovascular disease in adults.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States, accounting for about 610,000 - or 1 in 4 - deaths every year. CVD includes coronary heart disease and cerebrovascular disease, which ultimately result in heart attack and stroke, respectively.

Statins are a class of medicine commonly used to treat atherosclerosis, a condition where abnormally high levels of cholesterol have led to the building of plaques in the arteries. This can ultimately block the blood flow and usually leads to CVD. By treating atherosclerosis, statins help decrease the risk of stroke, heart attack, and chest pain.

Statins prevent the formation of cholesterol in the liver by blocking the enzyme HMG-CoA reductase, which is responsible for producing cholesterol.

According to the Centers for Disease Control and Prevention (CDC), the number of patients who have been prescribed statins has increased in the past decade.

During 2003-2012, the percentage of adults over 40 years of age who had used statin medication in the preceding 30 days increased from 20 percent to 28 percent. Overall, the use of statins has increased from 18 percent to 26 percent, with the average age of the patients also increasing over time.

After considering the evidence for both the benefits and the disadvantages of preventive statin use, the United States Preventive Services Task Force (USPSTF) have issued a new set of recommendations.

The USPSTF are an independent, volunteer panel of experts working in prevention and evidence-based medicine. The aim of the task force is to improve the health of Americans by making recommendations about clinical preventive practices, such as screenings, counseling, and other preventive medications.

The USPSTF recommendations are based on peer-reviewed evidence, and they were recently published in JAMA.

These guidelines include a grade B recommendation, which relates to patients who have a 10 percent or higher risk of developing a CVD event over the course of 10 years. In this case, a slow-to-moderate dose of statins should be offered to all adults aged between 40-75 years old without a history of CVD, but who have one or more risk factors for CVD, such as dyslipidemia, diabetes, hypertension, or smoking.

The new guidelines include a grade C recommendation for patients who have a calculated 10-year event risk of 7.5-10 percent of developing heart disease. In this case, the USPSTF recommend that doctors selectively offer low-to-moderate doses of statins to adults aged between 40-75 years without a history of CVD, but who have one or more risk factors.

Finally, the USPSTF do not have any recommendations regarding the use of statins in adults of 76 years of age and older, as they consider the evidence insufficient in this regard.

Evidence-based benefits and harms of statin therapy

The new recommendations are an update of the previous guidelines the USPSTF published in 2008.

In the meantime, the panel has revised the peer-reviewed evidence on the benefits and harms of certain screening and treatment practices.

They have assessed evidence on screening for and treating dyslipidemia in adults of 21 years of age and older and those without a history of CVD. They have also examined the evidence on whether the benefits of statins vary with dosage, clinical characteristics, or by demographic and clinical subgroups.

Their review found that the degree of benefit from statin therapy will be the greatest in people with the highest baseline risk of experiencing a CVD event.

The USPSTF analysis also revealed that the use of low-to-moderate statins reduces the risk of heart disease events, such as a heart attack or stroke, as well as the risk of death by at least a moderate amount. These results benefit adults aged 40-75 years with one or more CVD risk factors and a 10 percent chance of developing heart disease over a 10-year period.

A low-to-moderate dose also reduces the risk of CVD events and mortality by at least a small amount in adults aged between 40-75 years who have one or more CVD risk factors. These individuals would also have a 7.5-10 percent chance of developing a CVD event over a 10-year period.

Based on the evidence, the experts also established that the harms of low-to-moderate dosage of statins in adults aged 40-75 years are small.

Courtesy: medicalnewstoday.com

Author Index

ESCULAPIO
Vol. 12 No. 1-4 January-December, 2016
Review Article (RA), Original Article (OA), Case Report (CR) & Short Communication (SC)

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