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Cause of Anemia and Leucopenia

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Highlights

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Discovering Thoughts, Inventing Future

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Copper Deficiency: An Overlooked Cause of Anemia and Leucopenia

By Avneek Singh Sandhu, James Kim, Sivjot Binepal, Michael Gentry & Alejandro Calvo

Introduction- Copper deficiency (hypocupremia) is an acknowledged but often overlooked cause of anemia and leukopenia (1-4). It is recognized as a frequent cause of hypochromic microcytic anemia, leukopenia, and neuropathy. Copper deficiency anemia has been reported after gastric resection (e.g., Roux-en-Y) (1, 5, 6), excessive zinc consumption (1, 6-9), and in patients with short bowel syndrome receiving total parenteral or enteral nutrition lacking adequate copper supplementation (1, 2). We report a case of vitamin B12, and iron refractory severe anemia and leucopenia with history of Roux-en-Y surgery. Myelodysplastic syndrome was suspected. Bone marrow biopsy was consistent with copper deficiency and serum copper levels were undetectable. The patient experienced complete hematological recovery after copper replacement therapy.

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Copper Deficiency: An Overlooked Cause of Anemia and Leucopenia

Avneek Singh Sandhu [α], James Kim [σ], Sivjot Binepal [ρ], Michael Gentry [ω] & Alejandro Calvo [¥]

I. Introduction

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II. Case Presentation

A 63-year old female was evaluated due to an 18-month history of anemia, alopecia, dyspnea, difficulty with ambulation, and intermittent dizziness leading to recurrent near syncope. Complete blood count showed a hemoglobin of 7.4 g/dl, mean corpuscular volume of 80 fL. White blood cell count was 2,800/mcl, platelets were 249,000/mcl. B12 was low at 138 pg/ml. She had borderline iron deficiency with a ferritin of 66 ng/ml, total iron binding capacity of 475 ug/dl, and iron saturation of 6%.

She had a history of Roux-en-Y bariatric surgery 11 years prior and had been taking zinc supplementation prescribed by her bariatric surgeon.

She received 2 units of packed red blood cell transfusion; she was started on parenteral B12 as well as intravenous iron. Despite these supplementations, her cytopenias persisted, raising the possibility of myelodysplastic syndrome. A bone marrow biopsy was performed. Bone marrow core biopsy was normocellular for age (20%) with a normal myeloid to erythroid ratio. There were mild dyserythropoietic changes with rare ring sideroblasts (3 ring sideroblasts/100 erythroid precursor cells), rare nuclear contour irregularities, and cytoplasmic vacuolization of scattered erythroid precursors. The myeloid lineage showed scattered precursors, including myelocytes with cytoplasmic vacuolization (Figure 1). Rare atypical megakaryocytes with widely spaced nuclear lobes or multinucleation were identified. The morphologic findings in the erythroid and myeloid lineages were highly suggestive of copper deficiency/zinc toxicity, although they overlap with primary myelodysplasia, other sideroblastic anemias such as chronic alcohol toxicity, chronic inflammation, and lead poisoning. Her copper level was undetectable at<5 mcg/dl (Reference range: 70-175 mcg/dl) and her zinc level was elevated at 161 mcg/dl (Reference range: 60-130 mcg/dl). The patient was instructed to discontinue zinc supplements and was started on oral copper replacement therapy. Within four weeks, her hematologic parameters recovered completely (Figure 2).

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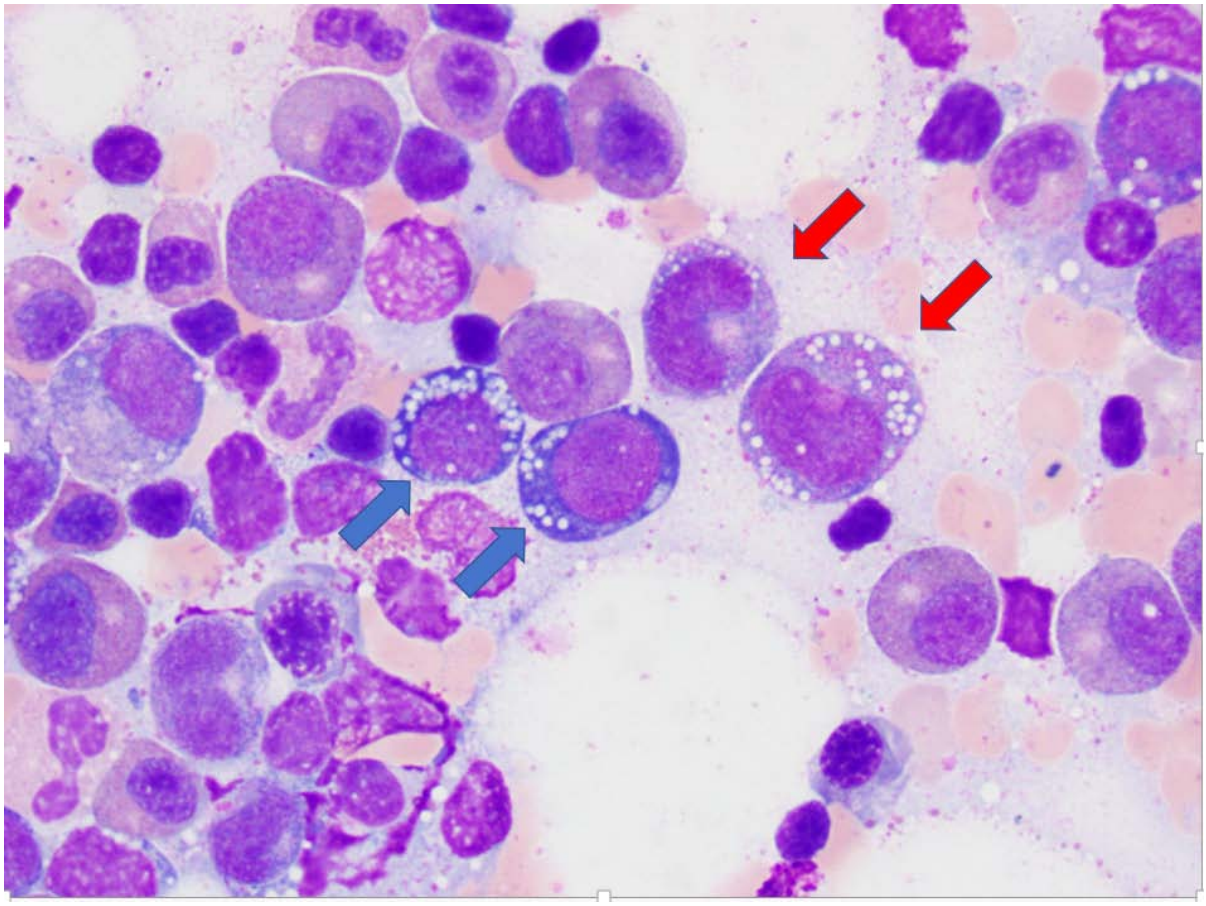


Fig. 1: Bone marrow aspirate showing cytoplasmic vacuolization of the erythroid (*blue arrows*) and myeloid lineages (*red arrows*), Original magnification 1000x

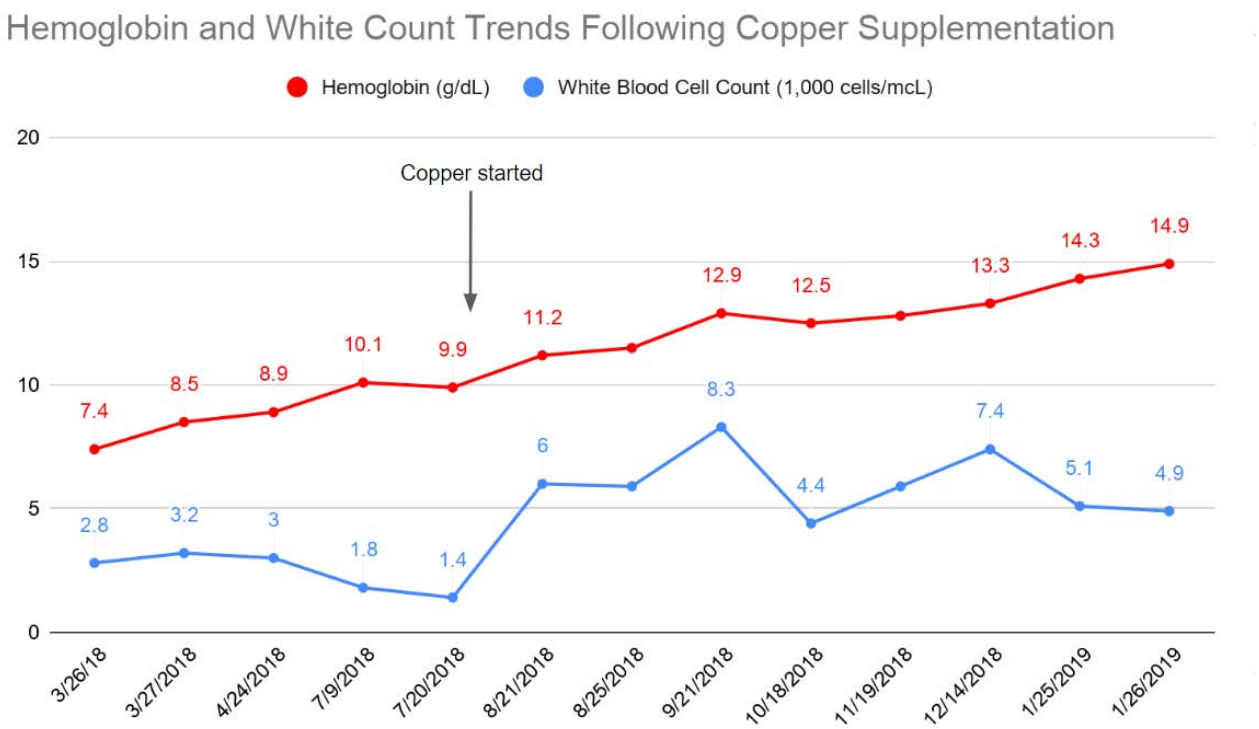


Fig. 2

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III. Discussion

Due to the high prevalence of obesity in developed countries, bariatric surgery has become increasingly popular. It is not well-known that gastric bypass procedures can cause acquired copper deficiency.

Hypocupremia is a commonly missed diagnosis in patients presenting with bi lineage cytopenias. Anemia and leukopenia can be seen. Anemia is usually microcytic, but cases of normocytic and even macrocytic anemia can be seen. Thrombocytopenia, however, is rare in copper deficiency (10). Physiologically, copper is absorbed in the gastric mucosa and proximal duodenum. The most common causes of hypocupremia are upper GI tract surgeries, especially bariatric procedures. Other causes include zinc toxicity, malabsorptive states, total parenteral nutrition, enteropathies associated with inflammatory bowel disease, and celiac disease. Hypocupremia due to a dietary deficiency is rare (11, 12).

A retrospective report of 40 patients with hypocupremia associated with hematologic abnormalities was reported by the Mayo Clinic (13). Ten patients were status post weight-reduction surgery, and 14 were status post other GI surgeries. Anemia and leukopenia were the most common hematologic abnormalities. Bone marrow studies revealed erythroid hyperplasia, vacuolization of pro-normoblasts, and myelocytes. Other reports also observed hepatic steatosis and myelopathy, resembling subacute combined degeneration secondary to vitamin B12 deficiency. Myelopathy is most likely caused by cytochrome-c oxidase dysfunction which is copper-dependent (11). Copper deficiency should be suspected in bariatric surgery patients who present with hematological disorders associated with neurological deficits (12).

Excessive zinc supplementation has to be significant, usually 50 mg/day or more, and prolonged to cause anemia. Previous studies have concluded that zinc and copper metabolism antagonize each other at the level of intestinal absorption through a family of proteins called metallothioneins (MTs). MTs are cystine-rich heavy metal-binding proteins that attach to certain metals and prevent their absorption by trapping them in intestinal cells. Zinc increases the synthesis of MTs in the enterocytes. Copper has a stronger affinity to bind with MTs. Because of this higher affinity and the MTs upregulation, copper absorption is decreased, and excretion is increased in the GI tract leading to hypocupremia (12, 14, 15).

Copper deficiency causes anemia due to defective iron mobilization. Metabolically, copper is involved in an intricate pathway, notably for erythropoietic activity. In enterocytes, hephaestin, a copper-dependent transmembrane protein, helps export iron from the gut into the circulation via transferrin. In hepatocytes, ceruloplasmin, which also binds with copper, facilitates iron transport from the liver to blood also via transferrin. In copper deficiency, hephaestin decreases, causing decreased enterocyte iron efflux. Iron transport from the liver to the blood would also fail. Ultimately, defects in these pathways would blunt iron's ability to reach the bone marrow for heme synthesis.

Copper deficiency may also lead to a low white cell count and increased susceptibility to infection. The mechanism of copper deficiency-induced leukopenia is not well understood. Proposed postulates include decreased survival of neutrophils or inhibited differentiation of CD34+ progenitor cells (16).

Our case report brings awareness about copper deficiency as one of the potential causes of hypochromic microcytic anemia and leukopenia. Knowledge about this nutritional deficiency is important in the setting of the growing population undergoing bariatric surgery. Copper deficiency can also cause peripheral neuropathy and myelopathy, leading to significant disability, which, if recognized late, can be irreversible. Therefore, prompt recognition and early treatment are key for successful treatment of neurological complications.

The current recommendation for oral copper supplementation is a loading dose of 8 mg of elemental copper each day for a week, 6 mg for the second week, 4 mg for the third week, and 2 mg daily afterward. And if an intravenous form is required, it is recommended to use 2 mg daily (administered over 2 hours) for five days and then intermittently as needed. If there is evidence of elevated zinc levels and excessive zinc ingestion, recommendations are to discontinue zinc supplements without changing copper dosing (17).

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Can we Rely on Transcutaneous Bilirbinometry during Phototherapy?

By Dr. Pearl Mary Varughese

Abstract- *Background:* Neonatal jaundiceis one of the main reasons for prolonged hospitalization in newborns, and its progress and treatment depends on serum bilirubin values. Phototherapy remains the mainstay of treatment of pathological jaundice in newborn babies. Though, transcutaneous bilirubinometer has been used as a screening device for measuring bilirubin, its role during phototherapy has always been questioned.

Objective: To study the correlation between Transcutaneous bilirubinometer (TcB) values with serum bilirubin levels (TSB) in infants during phototherapy in term and late preterm babies.

Materials and Methods: The study was conducted in a tertiary new-born center from November 2014 to June 2016. The inclusion criteria included all babies above 34 weeks gestation and exclusion criteria included babies with established direct hyperbilirubinemia, neonatal septicemia, major congenital/ gastrointestinal malformations, and those on phototherapy.

Keywords: *serum bilirubin, transcutaneous bilirubin, phototherapy, jaundice, rebound bilirubin, newborns.*

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Results: TcB and TSB showed good correlation (0.948) at 24 hrs of age before initiation of phototherapy but with a poor agreement (mean difference overestimating by 1.5mg/dl). The correlation was better for TcBE and TSB within 24 hours of phototherapy, and as the duration increased, the correlation for TcBC was better than TCBE and serum bilirubin. Bland Altmann shows good agreement too.

Conclusion: During phototherapy, transcutaneous bilirubinometry can estimate bilirubin better in covered regions when compared to exposed regions.

Keywords: serum bilirubin, transcutaneous bilirubin, phototherapy, jaundice, rebound bilirubin, newborns.

I. Introduction

Neonatal jaundice or hyperbilirubinemia is observed during the first week of life in approximately 60% of term and 80% of preterm infants(1). Neonatal hyperbilirubinemia occurs when there is an imbalance between the production and elimination of bilirubin, a breakdown product of hemoglobin. Kernicterus, which is due to severe hyperbilirubinemia, is the most easily preventable cause of neonatal mortality and brain death. With the increasing demand for a shorter length of hospital stay for babies after delivery, there is an increased risk of unrecognized or delayed hyperbilirubinemia resulting in an increased incidence of babies affected with kernicterus(2)

The problem of finding an accurate and specific method of bilirubin assay has for 50 years occupied the attention of many workers. In the early days, jaundice was assessed by the clinical evaluation of the babies. The conventional method of measuring serum bilirubin requires repeated blood sampling, which causes undue pain to the babies and emotional stress to the parents(3).Over the last three decades, transcutaneous bilirubinometry has emerged as a safe, simple, cost-effective non- invasive modality in the screening and monitoring of jaundiced newborns(4),(5). But its clinical utility is limited to a screening method rather than a replacement for invasive blood sampling.

Phototherapy has been widely used in pathological jaundice to reduce bilirubin levels. During phototherapy, frequent blood sampling is necessary to measure infants' bilirubin levels and to assess treatment efficacy to manage hyperbilirubinemia adequately (6). The usefulness of transcutaneous bilirubinometer (TcB) measurements during phototherapy in South Indian new-borns remain unclear. This study is being done to find out the correlation of transcutaneous bilirubinometer index (TcBI) with serum bilirubin levels in term and late preterm neonates during phototherapy and to study the reliability of TcBI during phototherapy in exposed and unexposed regions.

II. Methods

Study Population: This was a prospective observational study on inborn babies more than 34 weeks gestational age, from November 2014 to June 2016 in a neonatal unit of a medical college hospital in South India. The exclusion criteria included babies with established direct hyperbilirubinemia, neonatal septicemia, major congenital/ gastrointestinal malformations, and those started on phototherapy.

The sample size was calculated using the formula:

$$n = \frac{Z^2 * \{p(1-p)\}}{d^2}$$

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Z^2=1.96 at 95% confidence interval

P= proportion of infants with hyperbilirubinemia = 20%, d= error margin or precision=4%

The minimum sample required was 385. In the present study, 450 samples were collected. The study protocol was approved by the institutional review board and ethics committee. Written informed consent was obtained from the mothers for using their baby's de-identified data. Confidentiality was maintained throughout the study. The clinical and dimorphic profile of the mother and the baby was collected using a proforma.

Transcutaneous bilirubin levels (TcB) were estimated with Drager Jaundice Meter JM-105 by placing the instrument on the baby's sternum. The sternum was taken as the principal site of measurement, as several studies have shown excellent correlation with TSB compared to the other sites(7)(8). An average of three readings was taken as the TcB value. After each baby, the probe was cleaned with sterile gauze before using it for the next baby.

Approximately 1 ml of venous blood was collected in a microtainer clot activator tube for assessing total serum bilirubin (TSB) level under strict aseptic precautions after the mother was explained about the procedure. Serum bilirubin measurements were measured using the Diazo method (modified Jendrassik-Grof method) in the automated analyzer Cobas Integra 400 plus from Roche Diagnostics. The maximum interval of time between the transcutaneous measurement and the collection of blood for total serum bilirubin was 30 minutes.

A disposable temperature probe cover (Phoenix Medical Systems Ltd) was used as the phototherapy patch on the sternum of the babies. The patch was secured to the skin using liquid adhesive present on the inner surface and would remain in place till the end of phototherapy. The patch measures 32mm in diameter with a thickness of 2mm. (Figure 3)

All babies were visually examined every 6 hours on the first day of life by a trained physician and twice a day after that. At 24 hours TSB and TcB were done on all babies and later repeated as per attending clinician's discretion. If phototherapy is required, the babies were started on phototherapy after informed consent was obtained, and AAP guidelines were followed(9). Phototherapy lights used were the standard CFL 101 model (Phoenix Ltd) consisting of six CFL lights providing blue light at -30 $\mu W/cm^2/nm$ with an intensity of up to 40μW.A pre-set height of 45cm from the bed was made for the phototherapy lights. The eyes and genitalia of the babies would be covered before starting phototherapy. Phototherapy units are maintained and used according to manufacturer guideline. The phototherapy patch would be placed on the sternum, and the transcutaneous bilirubin measurements are taken from both the covered regions (area under the patch) and the exposed regions (the forehead of the baby). (Figure 4 and 5)

Four hours after the starting of phototherapy, the blood samples were taken for hemolytic work up according to the Department protocol. The phototherapy light would be switched off before the blood samples were taken. During phototherapy, whenever the blood sample was taken for bilirubin values, simultaneously the TcBI-E and TcBI-C measurements were also taken.

Data were entered in Microsoft Excel and analyzed using the SPSS version 20.0 for Windows software. Pearson's correlation and Bland Altman analysis were used for studying the data.

III. Results

The total number of babies delivered at the Pondicherry Institute of Medical Sciences during the study period (November 2014- April 2016) was 1950. 567 babies were recruited, and after taking into consideration the inclusion and the exclusion criteria, 450 babies were included considering be the incidence of hyperbilirubinemia to 20%. Of this, only 54 babies developed hyperbilirubinemia. (Figure 1)

The mean serum bilirubin of the entire cohort before phototherapy was 6.2 ± 1.4mg/dl, and the simultaneous mean TcB value was 7.7 ± 1.4mg/dl. In the 54 babies with significant hyperbilirubinemia, 23 babies (42.6%) were males, and 31 babies (57.4%) were females. In the 54 babies with significant hyperbilirubinemia, 10 babies (18.5%) were late preterm babies, and 42 babies (77.8%) were from 37-39 ^{6} weeks of gestation. Only 2(3.7%) babies were post-dated who developed significant hyperbilirubinemia.

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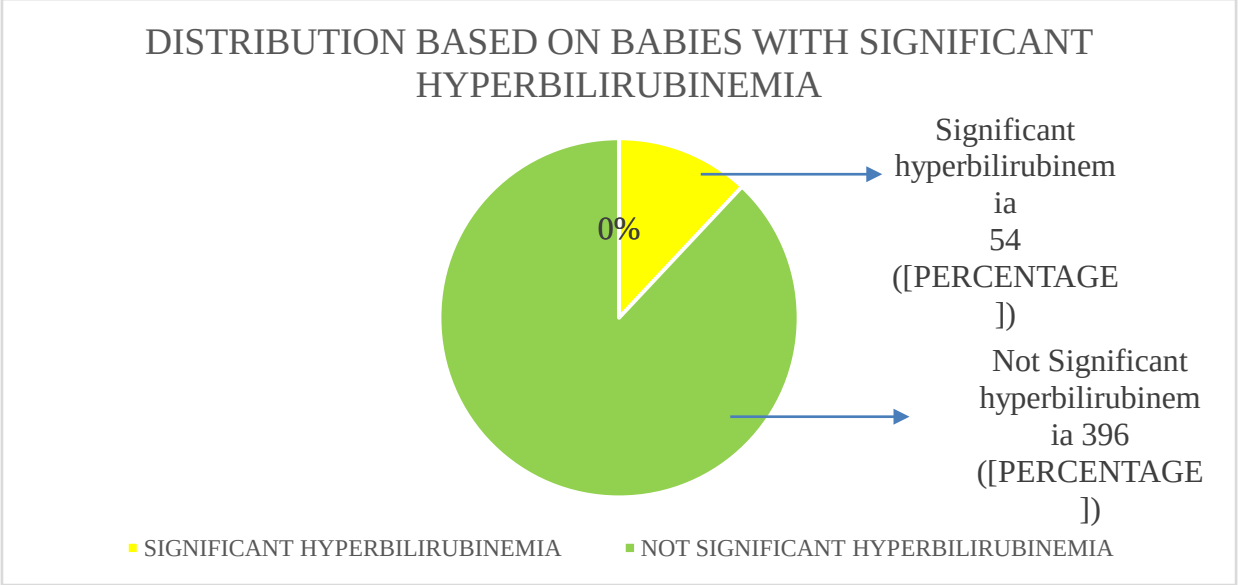


Figure 1: Distribution Based on Babies with Significant Hyperbilirubinemia

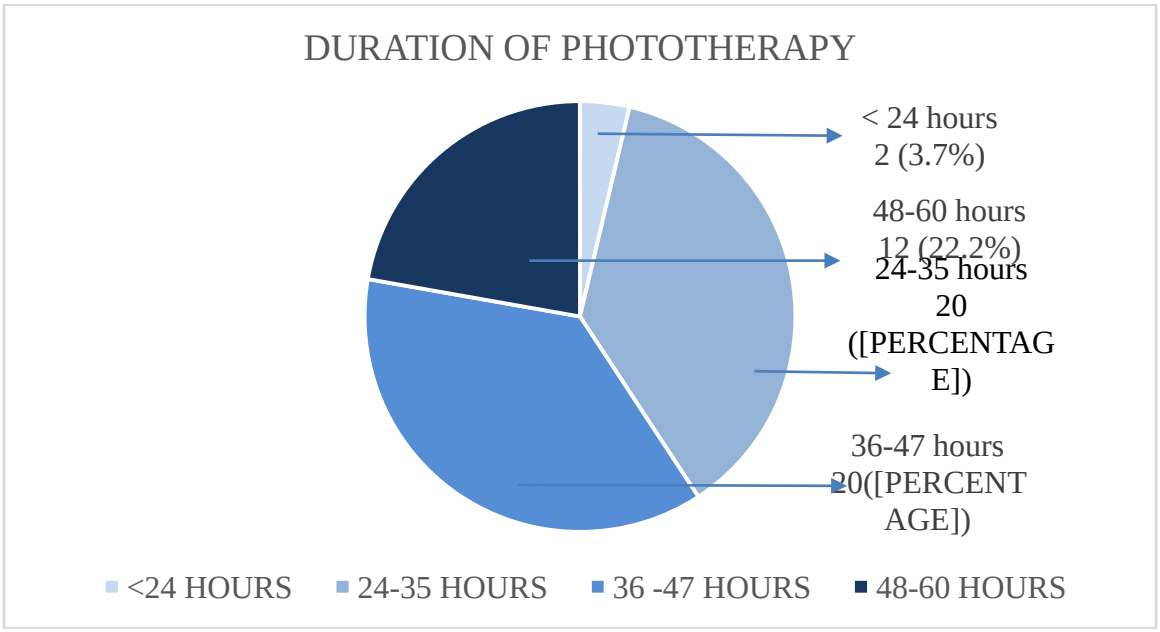


Figure 2: Distribution of Babies Based on Duration of Phototherapy

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Figure 3: Placing the patch on the sternum before phototherapy



Figure 4: Measuring TcBI C at the sternum after the patch is removed



Figure 5: Measuring TcBI E (Exposed) at the forehead of the baby

Table 1: Correlation of Tcbie (Exposed) and Tcbic (Covered) with Tsb at Different Time Intervals after Starting Phototherapy

Time		Number (%)	Correlation Co-efficient	Value
4 hours	TcBI-E (EXPOSED) WITH TSB	54 (100)	0.931	<0.001
	TcBI-C (COVERED) WITH TSB		0.886	
8-12 hours	TcBI-E (EXPOSED) WITH TSB	22 (100)	0.932	
	TcBI-C (COVERED) WITH TSB		0.885	
13- 24 hours	TcBI-E (EXPOSED) WITH TSB	39 (100)	0.980	
	TcBI-C (COVERED) WITH TSB		0.957	
25-36 hours	TcBI-E (EXPOSED) WITH TSB	6 (100)	0.829	
	TcBI-C (COVERED) WITH TSB		0.869	

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As shown in Figure 6, after 4 hours of starting phototherapy TcBI levels in both the covered and exposed regions showed good correlation with TSB (r= 0.931 and r= 0.886 respectively). After 8-12 hours of starting phototherapy, 22 babies were evaluated. The remaining 32 babies had lower risk, or the slower rise of bilirubin levels, so were pricked at a later time interval. There was a better correlation with serum bilirubin in exposed regions than covered regions within 12 hours of starting phototherapy with r= 0.932 and r= 0.885, respectively. As the duration of phototherapy increases, there was a significant correlation of TcB with TSB in both the exposed and covered regions (r = 0.980 in exposed regions and r= 0. 957 in covered regions). After 24 hours of starting phototherapy, though there is a significant correlation for both, the correlation was better in the covered regions (r = 0.829 in exposed regions and r= 0. 869 in covered regions). Further correlations as the duration of the phototherapy increases could not be done as there were very few cases.

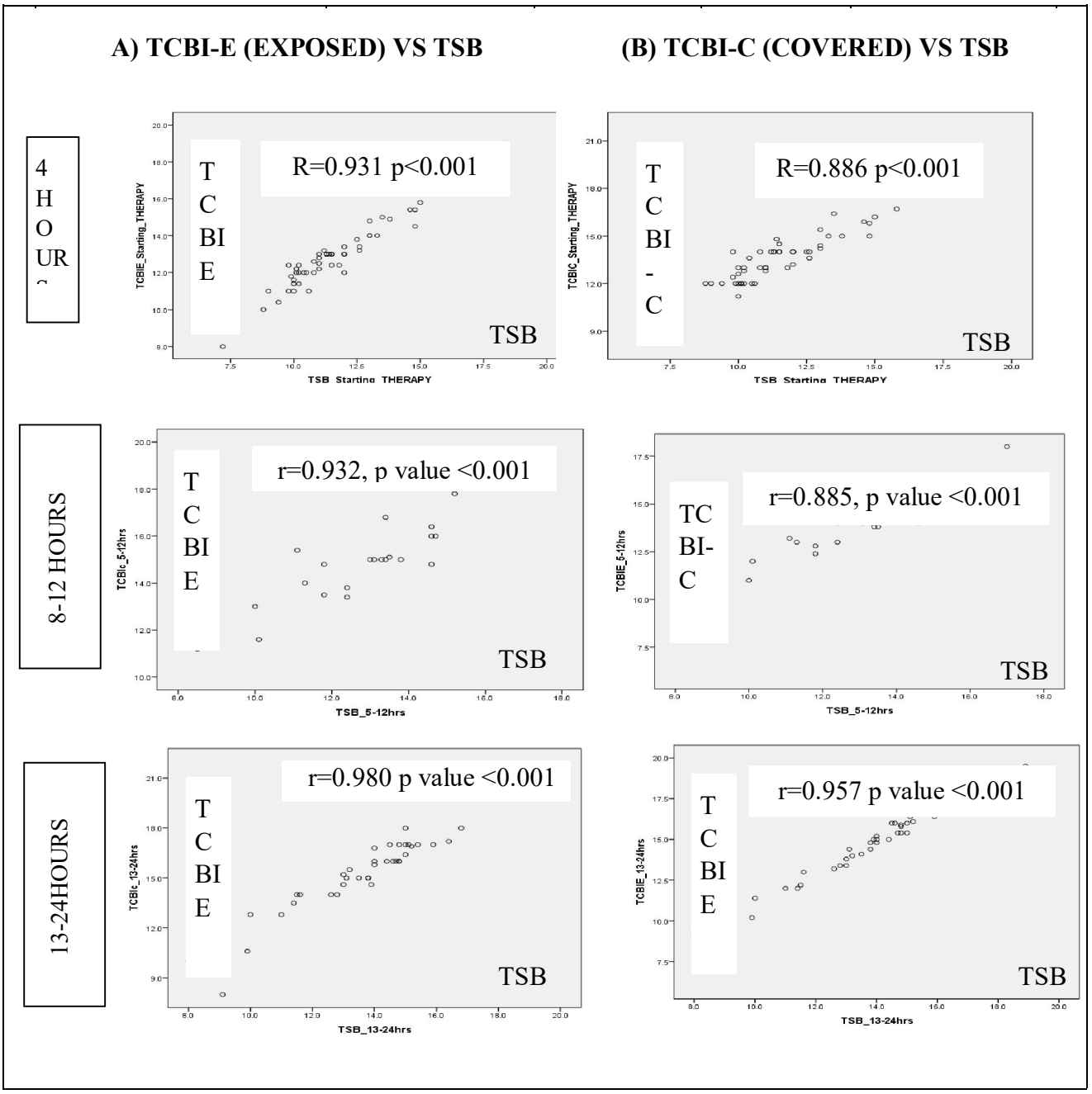


Figure 6: Graphs Showing Correlation of Tcbie and Tcbic with Tsb at Different Time Intervals during Phototherapy

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Table 2: Statistical Analysis According to the Bland Altman Plot for the Babies Who Had Significant Hyperbilirubinemia

TIME	VARIABLES	NUMBER (N)	MEAN (MG/DL)	STANDARD DEVIATION
4 hours after starting phototherapy	TcBI C with TSB	54	2.1	1.9
	TcBI E with TSB	54	1.3	0.6
13-24 hours after starting phototherapy	TcBI C with TSB	39	1.6	0.7
	TcBI E with TSB	39	0.7	0.6

As shown in table 2, 4 hours after starting phototherapy, the TcBIover- estimates TSB by 2.1 ± 1.9mg/dl in covered regions and by 1.3 ± 0.6mg/dl in exposed regions. Within 13-24 hours after starting phototherapy, the TcBI over- estimates TSB by1.6 ± 0.7mg/dl in covered regions and only by 0.7 ± 0.6mg/dl in exposed regions.

IV. Discussion

Transcutaneous bilirubinometry has been extensively used as a substitute for serum bilirubin as it is reliable, safe, quick, and cost- effective. But when the babies are subject to phototherapy, serum bilirubin continues to be the ideal choice of many pediatricians for assessing the progression of jaundice. There have been conflicting ideas when the correlation of transcutaneous bilirubin and serum bilirubin during phototherapy has been discussed with differing characteristics like the site of assessment, covered and exposed regions, type of lights, and type (continuous or intermittent) of phototherapy. With the initiation of phototherapy, a rapid decrement in dermal bilirubinis caused by photoisomerization ofalbumin-bound bilirubin in interstitial places and subcutaneous capillaries intolumirubin and other photo isomers (10). Studies have shown that the rate of decrease of dermal bilirubin as measured by TcBI is non – linear concerning the duration of phototherapy. Serum bilirubin shows an exponential decline that is independent of the logarithm of light dose. Skin bilirubin decreases more than the plasma bilirubin causing the bilirubin gradient between the two. The possible rationale behind the difference in shielded and exposed regions could be that TcB in exposed regions underestimates bilirubin levels owing to bleaching with phototherapy while dermal bilirubin at the shielded site, doe not participate in the phototherapy induced conversion of bilirubinto its photo isomers as much as the exposed skin (11). Vogl et al. using Gosset's icterometer, showed that light does not bleach the covered skin, and a clear demarcation exists between bleached and icteric skin(12).

With the forehead being covered, Zecca et al. concluded that transcutaneous bilirubin measurement of covered skin could be a reliable method for use during phototherapy, reducing blood sampling(13). Mitra Radfaretal. too proved that post-phototherapy correlation was 0.92 among term and 0.887 among preterm neonates in patched area (forehead), while it was 0.666 among term and 0.756 among preterm neonates post-phototherapy in unpatched areas(14). Most of the studies show that the covered regions had a better correlation to serum bilirubin values during phototherapy compared to the exposed regions in both term and preterm babies(15) (16) (17) (18).But a systemic review conducted showed that there was no statistically significant difference in the pooled estimates of the correlation coefficients in the covered regions and the exposed regions (r= 0.71 and 0.65 respectively)(19). But these results were conflicting to the results obtained by a few authors who proved that TcB could not be used as a surrogate measure of TSB once phototherapy has started (20). Murli et al. did notfind agreement between TcB and TSB in 34- 41week gestation neonates receiving phototherapy (21). Fok et al. and Tudehope et al. reported a lower correlation between TcB and TSB both in the exposed and unexposed areas of the skin of the forehead in term neonates receiving phototherapy (22) (23).

In our study though there is a statistically significant difference, the correlation is found to be better in exposed regions in the first 24 hours, and after 24 hours, the correlation not only decreased but is found to be better in covered regions than exposed.

This study was the first of its kind to be done in the South Indian population. Most of the studies showed correlation coefficients, but we have used both correlation coefficients and Bland Altman plots. Bland Altman plots do not depend on treatment thresholds and are more useful than correlations in clinical practice. But there were a few limitations in our study. Firstly, it is not a population-based study, and it represents the data of a single tertiary care hospital in South India. The sample size was small compared to other studies.

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Lastly, further correlations as the duration of the phototherapy increases (after 36 hours) could not be done as there was very few cases.

V. Conclusion

Significant correlations exists between TcB and serum bilirubin levels in both the exposed and covered group. But the exposed group is overestimating the bilirubin level at different points of time more than that of the covered group. Hence the TCB prediction of bilirubin is better in covered areas when compared to exposed areas after 24 hours of starting phototherapy.

Conflict of Interest: There was no conflict of interest.

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Recruiting the Human Pathological Specimen Scientifically and Rightly for Cancer Molecular or Biological Researches

By Xu Han-You

Abstract- Background: Recruiting the human pathological specimen is very important for cancer researches. But there is no quality control of recruiting the human pathological specimens on cancer genetics researches in China and other countries at present.

Methods: In this article, the author researched and provided facts and examples obtained from studies conducted in high grade institutes in China and others that the quality control of recruiting the human pathological specimens in cancer genetics researches are not treated with attention. In order to mend these problems, different methods for the recruiting of the human pathological specimen better have been created.

Findings: At least some research projects have not paid attention to the quality control of recruiting the human pathological specimens in cancer genetics researches in high grade institutes from China and others.

Keywords: recruiting the human pathological specimen; cancer research; genetics; research promotion; quality control; S T R E G A.

GJMR-F Classification: NLMC Code: QU 110



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Recruiting the Human Pathological Specimen Scientifically and Rightly for Cancer Molecular or Biological Researches

Xu Han–You

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Methods: In this article, the author researched and provided facts and examples obtained from studies conducted in high grade institutes in China and others that the quality control of recruiting the human pathological specimens in cancer genetics researches are not treated with attention. In order to mend these problems, different methods for the recruiting of the human pathological specimen better have been created.

Findings: At least some research projects have not paid attention to the quality control of recruiting the human pathological specimens in cancer genetics researches in high grade institutes from China and others. The research creates and provides 7 methods and directions on how to recruit the human pathological specimens scientifically and rightly. The most important method to recruit the human pathological specimen well is that, before recruiting the human pathological specimens in cancer patients, the histories of X-ray examinations, the examinations of the computed tomography, the chemo-therapy and the other treatment methods should be considered carefully. Because the X-ray, chemo-therapy and other radiation may heavily damage the structure of chromosomes and genes. So we must consider these things before the genome-wide association study and other cancer molecular or biological researches began.

Interpretation: If the cancer molecular or biological researches consider and reference these viewpoints before their researches. The bad situation of quality control of recruiting the human pathological specimens could be changed into better. So that the quality of the cancer researches could be promoted and enhanced a lot. The cancer prevention and treatment could be better. The author proposed to add an extension of the S T R E G A statement.

Funding: The funding of this research project was supported by author himself. There is no conflict of interest for this paper.

Keywords: recruiting the human pathological specimen; cancer research; genetics; research promotion; quality control; S T R E G A.

I. Introduction

Recruiting the human pathological specimen scientifically and rightly should be very important for medical and biological researches. It is known to all medical and biological researchers that up to now, lots of recruiting the human pathological specimen have been done and lots of researches have been recruiting the human pathological specimen, including clinical and basic researches. Many high quality journals have published lots of research articles which recruited the human pathological specimen, especially the cancer researches.

As more and more cancer genetics researches have been done by recruiting the human pathological specimen. And more and more these kinds of researches are under way. Also, more and more cancer genetics researches are going to be done by recruiting the human pathological specimen. The quality control in the cancer genetics researches is the most important aspect. One of the important factors of the quality control is the quality control of recruiting the human pathological specimens which are used in these research projects for cancer genetics researches. As the genome-wide association study applies more and more human pathological specimens of cancer patients. Recruiting the human pathological specimens scientifically and rightly is the top agenda of the research quality control. But there is little report about the method of recruiting the human pathological specimens scientifically and rightly for cancer molecular or biological research in the cancer genetics research articles. Which expresses that it is imperative to pay more and more attention to this problem. In this review, I research and provide the fact that there are at least some research projects that have not paid attention to the quality control of recruiting the human pathological specimens in cancer genetics researches in high grade institute in China and others. And provide the methods and directions on how to recruit the human pathological specimens scientifically and rightly.

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II. The Fact of no Quality Control of Recruiting the Human Pathological Specimens in China

a) Some research projects searched have not quality control of recruiting the human pathological specimens in China

In one of the top cancer institute of China, the cancer genetics researches have no quality control of recruiting the human pathological specimens. But the articles of their researches have been published on the Nature Genetics and other high level cancer related journal. For example, in the research of Chen Wu, *et al* [1], they conducted a genome-wide association study (GWAS) and a genome-wide gene-environment interaction analysis of esophageal squamous-cell carcinoma (ESCC) in 2,031 affected individuals (cases) and 2,044 controls with independent validation in 8,092 cases and 8,620 controls. They identified nine new ESCC susceptibility loci, of which seven, at chromosomes 4q23, 16q12.1, 17q21, 22q12, 3q27, 17p13 and 18p11, had a significant marginal effect ($P = 1.78 \times 10-39$ to $P = 2.49 \times 10-11$) and two of which, at 2q22 and 13q33, had a significant association only in the gene–alcohol drinking interaction. The Nature Genetics published an article that involved 10123 cases of esophageal squamous-cell carcinoma sample and 10664 control sample. There is not any clear method report on how recruiting the human pathological specimens of 10123 cases of esophageal squamous-cell carcinoma (ESCC) sample. Also, there is not any clear method report on how recruiting the human specimens of 10664 control sample and also they say nothing of the quality control of recruiting the human pathological specimens. Even the genome-wide of the 10123 cases of esophageal squamous-cell carcinoma sample had been attacked or have been attacked by X-ray, chemo-therapy and other radiations or damages from repeated treatments and examinations. Furthermore, the history facts of X-ray, chemotherapy and other radiations or damages from examinations in 10664 control sample are confused. So it is much too easy to arouse the questions that if their research finding of nine new ESCC susceptibility loci have been caused by X-ray, chemo-therapy and other radiations or damages from repeated treatments and examinations applied on the ESCC patients before the research recruiting the human pathological specimens of 10123 cases of esophageal squamous-cell carcinoma.

In this top cancer institute of China, the other similar researches present the same situations or problems with no quality control of recruiting the human pathological specimens. The researches are studies of Chen Wu, et al. [2], research of Gao, Y. et al. [3] and Christian C Abnet, et al. [4], Meiying Li. et al.[5].

In an other institute, one of the research presents also the similar situation. In the research of Zi-Jiang Chen, et al [6]., they conducted genome-wide association study identified susceptibility loci for polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3. In their study, they only recruited from Han Chinese women presenting in reproductive and gynecology clinics in several collaborating hospitals. In all subjects from whom peripheral blood samples were obtained, they recorded such anthropometric variables as age, body height, weight and menstrual cycle, as well as selected endocrine and biochemical parameters. All polycystic ovary syndrome cases were diagnosed according to the Revised 2003 Consensus on Diagnostic Criteria and Long-term Health Risks Related to Polycystic Ovary Syndrome. But no quality control of recruiting the human pathological specimens was done. The quality control of recruiting the human pathological specimens in this study is excluding the damages of venous peripheral blood lymphocytes samples caused by X-ray or other physical and chemicals.

b) Some research projects searched have not quality control of recruiting the human pathological specimens in other country

It is the fact that the methods of the cancer genetics researches and genome-wide association study (GWAS) are all referenced methods of foreign countries, even in the top institutes in China. So the worse situation that no quality control of recruiting the human pathological specimens in China is infected each other among the foreign institutes and the institutes of China. This important aspect is supported by the fact that the top biological journal, the Nature Genetics, has been constantly publishing the research articles with no quality control of recruiting the human pathological specimens from China and foreign institutes.

At present, even the so called highest level in the world about the Pan-cancer analysis of whole genomes (PCAWG) also has shortcomings in recruiting cancer specimens. Because the research has only paid attention to the samples come from treatment-naive, primary cancers. But they have not scientifically and rightly paid attention to if their samples come from treatment-naive, primary cancers had diagnosis X-ray and other diagnosis damages to the genes of the samples [7]. And lots of researches have been referencing the samples doing as what the PCAWG has done.[8, 9].

c) Some research projects searched have not quality control based on S T R E G A and other international guidelines.

According to the guidelines of S T R E G A (Strengthening the Reporting of Genetic Associations), [10, 11]. the Consolidated Standards of Reporting Trials (CONSORT) [12, 13], and the Strengthening the

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Reporting of Observational studies in Epidemiology (STROBE) Statement [14, 15], some research projects searched in China have not quality control based on these international guidelines. Especially, these research projects have not population stratification about the disease risks. Their genome-wide association studies also have not either family-based designs or methods such as genomic control and principal components analysis to control for stratification. They say nothing about the research designs or methods to control the stratification of risk factors in research, diagnosis and treatment of the cancer patients, especially the risk factors of radiation and chemicals.

III. Methods and Directions on how to Recruit the Human Pathological Specimens Scientifically and Rightly

As the situation that no quality control of recruiting the human pathological specimens in China and other countries are severe. It is imperative to mend and change the bad situation at once. Because I am a medical professional and researcher. I can not help but do the research on these things. So the methods and directions on how to recruit the human pathological specimens scientifically and rightly have been researched as follows.

a) The time to recruit human pathological specimens in cancer patients and normal control groups should be in the same period. Because the human pathological specimens are easy to lose their structure of chromosomes and genes.
b) The position, where the human pathological specimens in cancer patients are recruited, should be the same as the normal control groups. Because the molecular pathology or molecular histopathology are different in various position from cancer patients and normal control groups.
c) The past human pathological specimens in cancer patients should not be used for cancer genetics research. Because the past human pathological specimens in cancer patients must be changed by environment and its own changes can develop as time goes on.
d) The top important thing is that before recruiting the human pathological specimens in cancer patients, the histories of X-ray examinations, examinations of the computed tomography, chemo-therapy and other treatment methods should be considered carefully. Because the X-ray, chemo-therapy and other radiation may heavily damage the structure of chromosomes and genes. So if we did not consider these things before the genome-wide association study and other cancer molecular or biological researches began. There was no way to do the scientific researches.
e) As radiotherapy is the most important therapy for cancer patients. The human pathological specimens from the cancer patients are often interfused with the heavy radiations. How to research scientifically and rightly on these pathological specimens are more important than finding new susceptibility loci in cancer patients.
f) The fixation, staining preparation, section and preservation of the specimens are also important. So the method for fixation, staining preparation, section and preservation of the specimens should be the same between the cancer patients and normal control groups.
g) The health examination of cancer patients and normal control groups by X-ray, computed tomography and other examinations should also be considered carefully before research.

IV. Discussion

The rapidly evolving evidence on genetic associations is crucial to integrating human genomics into the practice of medicine and public health. Genetic factors are likely to have an impact on the occurrence of numerous common diseases, and therefore identifying and characterizing the associated risk, or protection, will be important in improving understanding of etiology and potentially for developing interventions that might be based on genetic information.

The number of publications on gene-disease associations has increased tremendously, with the number each year having more than doubled between 2001 and 2007, with more than 30,000 published articles during that time. Articles on genetic associations have been published in about 1500 journals, in several languages.

Although there are a number of similarities between genetic association studies and “classical” observational epidemiologic studies of lifestyle and environmental factors, the former present several specific challenges including an unprecedented volume of new data and the likelihood of very small individual effects. Genes may operate in complex pathways with gene-environment and gene-gene interactions. Moreover, the current evidence base on gene-disease associations is fraught with methodological problems. These include inadequate statistical power; flawed study design; suboptimal study conduct and biased analyses; lack of standardization among studies; selective reporting of “positive” results; and poor or incomplete reporting of results even from well-conducted studies [10, 11].

Hopefully, the CONSORT, STROBE, and S T R E G A have highlighted the importance of quality control in recruiting the human pathological specimens on cancer clinical molecular diagnostic tests and basic molecular or biological researches.

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V. Conclusion

In order to mend the problems which there is no quality control of recruiting the human pathological specimens on cancer genetics and other biological researches in China and other countries at present. The methods how to do the better and recruit the human pathological specimen well have been created.

The research has found that at least some research projects have not paid attention to the quality control of recruiting the human pathological specimens in cancer genetics researches in high grade institute in China and others. The research creates and provides 7 methods and directions on how to recruit the human pathological specimens scientifically and rightly. The most important method to recruit the human pathological specimen well is that, before recruiting the human pathological specimens in cancer patients, the histories of X-ray examinations, the examinations of the computed tomography, the chemo-therapy and the other treatment methods should be considered carefully. Because the X-ray, chemo-therapy and other radiation are heavy damage to the structure of chromosomes and genes. So if we did not consider these things before the genome-wide association study and other cancer molecular or biological researches began. There was no way to do the scientific researches.

If all the genome-wide association study and other cancer molecular or biological researches consider and reference my viewpoints before their researches. The bad situation of quality control of recruiting the human pathological specimens could changed into better. So that the quality of the cancer molecular or biological researches could be promoted and enhanced a lot. The advancing of the cancer prevention and treatment could be great.

This work may be referenced to be an extension of the S T R E G A statement and should be used to guide the research designs or methods to control the stratification of risk factors in the processes of diagnosis and treatment of the cancer patients, especially the risk factors of radiation and chemicals and to recruit the human pathological specimens rightly on cancer clinical molecular diagnostic tests and basic molecular or biological researches.

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Conflict interest statement:

There is no conflict of interest for this paper.

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Integrated use of the GeneXpert Platform for TB, HIV and EVD Testing in Liberia

By Kassaye Tekie Desta, John B. Dogba, Julia Toomey Garbo, Dedeh B. Kessely, Candace B. Eastman & Jerry G. Daboi

Abstract- *Background:* The capacity for molecular testing of the Human Immunodeficiency Virus (HIV) Viral load, Tuberculosis (TB) and epidemic- prone disease was very limited in Liberia prior to the Ebola Virus Diseases (EVD) outbreak. The use of point of care and near point of care machines for multiple disease testing of HIV, TB and EVD was adopted as a solution to these challenges. The purpose of this study was to evaluate the integrated use of GeneXpert for the three disease testing.

Methods: A previously collected and reported GeneXpert testing data was used to evaluate the integrated use of the GeneXpert platform for TB, HIV viral load and EVD testing. All the laboratory GeneXpert secondary data available since the machines were installed and started testing were analyzed.

Keywords: *GeneXpert, EVD, HIV, viral load, TB.*

GJMR-F Classification: *NLMC Code: QW 168.5.H6*

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Kassaye Tekie Desta [α], John B. Dogba [σ], Julia Toomey Garbo [ρ], Dedeh B. Kessely [ω], Candace B. Eastman [¥] & Jerry G. Daboi [§]

Abstract- Background: The capacity for molecular testing of the Human Immunodeficiency Virus (HIV) Viral load, Tuberculosis (TB) and epidemic- prone disease was very limited in Liberia prior to the Ebola Virus Diseases (EVD) outbreak. The use of point of care and near point of care machines for multiple disease testing of HIV, TB and EVD was adopted as a solution to these challenges. The purpose of this study was to evaluate the integrated use of GeneXpert for the three disease testing.

Methods: A previously collected and reported GeneXpert testing data was used to evaluate the integrated use of the GeneXpert platform for TB, HIV viral load and EVD testing. All the laboratory GeneXpert secondary data available since the machines were installed and started testing were analyzed. Besides; Field observation report on the operation, coordination and impact of the integrated testing programmatic intervention was included.

Results: The integrated testing of HIV Viral load, Mycobacterium Tuberculosis/Rifampicin (MTB/RIF) and EVD using the GeneXpert platform has played a significant role in Liberia. A total of 706 HIV viral load, 3695 MTB/RIF and 2309 EVD GeneXpert tests were conducted since the start of the integrated testing.

Conclusion: The integrated use of the GeneXpert platform for TB, HIV and EVD is very crucial as it helped in enhancing the services and coordinating resources in a sustainable way. Lessons learned from this integration will help to effectively scale up the integrated testing.

Keywords: GeneXpert, EVD, HIV, viral load, TB.

I. Introduction

The EVD outbreak in Liberia began in March 2014 and has had a devastating impact on the health system. The health system was ill- equipped to effectively respond to the epidemic. The laboratory diagnostic service was one of the health services which was affected by the EVD outbreak [1]. During the outbreak, laboratory services like other health services component had to come to a standstill. This was mainly due to the lack of laboratory reagents and consumables. The laboratory system of Liberia in the pre- Ebola era was weak and lagged behind the other component of the health services. Even though the National Diagnostic Unit of Liberia was established in 2009 and laboratory policy was developed in 2011, the laboratory subunits in the Ministry of Health including the National Reference Laboratory, the National Diagnostics Unit and the National Blood Safety Program, were not well coordinated and operated as separate units. The laboratory testing service was limited to hospitals, health centers and clinics. There was no specialized and molecular testing capacity at the national reference laboratory which was providing limited testing services for epidemic-prone diseases such as measles, rubella and yellow fever [2, 3].

The lack of in-country molecular and specialized testing capacity critically affected the epidemic- prone disease testing as well as specialized clinical testing in Liberia. Some of the services which were affected by the lack of the molecular testing capacity were HIV viral load, HIV early infant diagnosis testing, TB, Lassa fever, Dengue, Marburg and other hemorrhagic fevers. It was only at the end of 2013 that the first molecular testing capacity was established at the national reference laboratory of Liberia. Prior to 2013, Liberia used to send HIV 1 specimens to South Africa for polymerase chain reaction molecular testing. The average Turnaround Time (TAT) was 30 to 45 days. The first molecular testing capacity was initiated at the national reference laboratory of Liberia by the coordinated effort of the Clinton Health Access Initiative (CHAI) Liberia office and the National AIDS Control Program (NACP) of Liberia. A standard molecular laboratory for specimen extraction, master mixing and amplification/detection was established for HIV molecular testing. This was funded by the Global Fund. The testing service for HIV was interrupted and the laboratory was dedicated for EVD testing; following the Ebola outbreak in March 2014. This was the only molecular laboratory in Liberia that could be potentially used for EVD testing. The dedication of the molecular laboratory for EVD testing interrupted the HIV clinical molecular testing. During the EVD outbreak; the HIV molecular testing was not restored for more than one year. The interrupted molecular tests include HIV 1 early

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infant diagnosis and HIV viral load testing. Patients on Anti-Retroviral Therapy (ART) should be monitored for treatment response using viral load test [4]. Despite this, developing countries manage patients by CD4 cell counts and clinical staging as result of the expensive equipment and skilled manpower required by the current viral load assays [5].

According to 2013 Liberian Demographic and Health Survey, the prevalence of HIV in the general population aged 15-49 was 2.1% (1.9% HIV 1 and about 0.3% HIV-2). In 2015, an estimated 26,313 adults and 2,339 children were living with HIV respectively. The percentage of eligible people receiving ART were 25.8% only [6]. The lack of capacity for HIV molecular testing, the low testing volume as result of the 2.1% low prevalence of HIV and the poor specimen referral linkage are the fundamental reasons for the adoption of point of care and near point of care devices in Liberia. As a good opportunity to this, the Xpert HIV-1 Viral Load (Cepheid) cartridge was launched in 2014 as a potential point-of-care rapid viral load assay [7]. The release of the EVD and HIV viral load GeneXpert assays from Cepheid in 2014 followed by Ministry of Health of Liberia approval for use in 2015 was a very crucial opportunity for Liberia.

The GeneXpert instrument system is an automated and integrated cartridge-based system for sample purification, nucleic acid amplification and detection of target in clinical specimens using real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR). Several infectious agents can be detected using the technology and appropriate cartridge including EVD, HIV Viral Load, HIV Early Infant Diagnosis (EID), MTB and rifampicin resistant strains. The GeneXpert platform offers module sizes of 1 to 64 which facilitates placement of the technology across the entire health system tier. The GeneXpert can be used outside of central reference laboratories and is ideal when placed at district and even sub-district levels [8].

In July 2017, the HIV-1 viral load cartridge received the World Health Organization (WHO) pre-qualification [7]. The GeneXpert viral load assay is the most needed and market attractive diagnostic tool in resource-constrained settings as result of the minimal training and infrastructure requirement. Country-level validation studies have been conducted on the accuracy of the GeneXpert viral load assays in a variety of settings. All reported correlations between the Xpert HIV-1 viral load assay and gold-standard tests were very high and indicated a very high degree of agreement between Xpert viral load and reference standard viral load values [9]. Despite the recommendations put forward by the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, viral load monitoring of ART is not routinely performed in Liberia [10]. The national ART guideline of Liberia also recommends viral load testing for monitoring of treatment failure for all patient categories.

EID was initiated in Liberia in 2013 at the national reference laboratory of Liberia using Roche reagent. However, it was interrupted by EVD outbreak as the molecular laboratory used for EID was dedicated to EVD testing. A decentralized EID testing is very critical in low volume and resource constrained setting. The placement of the GeneXpert machines also considered the EID testing. During 2015, a total of 71,891 pregnant women were tested for HIV and 2122 of them were HIV positive. Out of the 1684 infants born from HIV positive mothers, only 346 were EID tested in 2011 [6].

The GeneXpert MTB/RIF assay on the GeneXpert molecular system, which was endorsed by WHO in 2010, is the first GeneXpert TB assay released for clinical testing in resource-limited settings and the most scaled-up new TB technology [11]. Liberia adopted a 4 modules GeneXpert technology for testing MTB/RIF assay in 2013 with two machines installed at the TB annex hospital and the Ghanta TB/leprosy rehabilitation center. The machines were procured by the Global Fund office in Liberia and the installation and training were conducted by CHAI and the National Diagnostics Unit of Liberia. The GeneXpert technology was introduced as a diagnostic test in individuals suspected of Multi-Drug Resistant (MDR) TB. In 2015, the national TB program TB testing algorism was revised to include GeneXpert for smear-negative TB cases and for HIV associated TB. The Tuberculosis culture and drug susceptibility testing laboratory was not fully operational, and adoption of MTB/RIF assay was very timely to detect MDR suspected cases in Liberia.

According to the WHO report of 2017, the TB incidence in Liberia for the year 2016 was 308/100,000 population. The total number of patients diagnosed with TB was 7180 in 2016. The percentage pulmonary TB case is 70% of all the notified TB cases and only 60% of the pulmonary cases were bacteriologically confirmed. The MDR-TB burden is unknown in Liberia as there has been no national drug resistance survey conducted. According to the 2017 WHO TB report, the estimated MDR/RR-TB was 2.6% in new cases and 18% in previously treated cases respectively. TB diagnosis in Liberia has been mainly based on sputum smear microscopy [12]. The sensitivity and specificity of sputum microscopy are very low.

To improve the TB diagnosis in Liberia, the introduction of GeneXpert technologies with higher sensitivities and specificities is crucial. The pooled sensitivity of GeneXpert MTB/RIF assay is 88% and 68% when used as an initial diagnostic test replacing smear microscopy and as an add-on test following a negative smear-microscopy result respectively. The pooled specificity is 99% in both cases. When used to detect rifampicin resistance, GeneXpert MTB/RIF assay

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achieved a pooled sensitivity of 95% and a pooled specificity of 98% [13].

One of the lessons learned from the 2014 outbreak of EVD was the importance of rapid and accurate diagnosis of new and re-emerging diseases and the challenges around diagnostic testing to address these diseases. Throughout the 2014-2015 outbreak, EVD testing was limited to sophisticated biocontainment laboratory facilities, leading to challenges with specimen collection, data management and often a prolonged TAT to final results. In an outbreak setting, it was very difficult to manage the high number of specimens with this setup. Poor specimen referral network, lack of trained workforce and poor result reporting system were some of the challenges faced during the EVD outbreak. As a result of these challenges, the need for rapid test, point-of-care and near point of care EVD testing was evolved [14]. It was with this initiative that the GeneXpert EVD assay was developed for use in 2015.

WHO included Cepheid's GeneXpert Ebola test to its list of Ebola diagnostics with emergency use authorization on the 8th May 2015 [15]. Following the WHO acceptance, The GeneXpert Ebola test also received the United States Food and Drug Association (FDA) approval in March 2015 [16]. The Ministry of Health of Liberia approved the EVD assay in September 2015 with support from WHO, Foundation for Innovative New Diagnostics (FIND), Academic Consortium to Combating Ebola in Liberia (ACCEL), United States Centre for Disease Control and Prevention (CDC) and other stakeholders. The GeneXpert for EVD was used at the modular laboratory at Eternal Love Winning Africa (ELWA) in biosafety level three laboratories during the EVD outbreak [17].

When Liberia was declared free of EVD, WHO and ACCEL brought additional GeneXpert machines. The EVD GeneXpert machines have been in use for EVD surveillance testing with limited tests per day. The underutilization of these machines as well as the critical molecular testing challenges of HIV and TB program were the driving force for the integrated use of the GeneXpert platform in Liberia. Despite the effort of the NACP to initiate in-country capacity for HIV molecular testing, the dedication of the HIV molecular laboratory for EVD testing and the expiration of the reagents negatively impacted the HIV molecular testing service in Liberia. The TB program as well couldn't conduct enough tests using the four GeneXpert machines. EID was also considered in the integrated testing as it was interrupted during EVD outbreak. GeneXpert EID testing training was provided together with the HIV viral load GeneXpert training using whole blood but it was not included in our study as there was a prolonged delay in the procurement of HIV EID cartridges, heat block and Dried Blood Spot (DBS) bundles. When EID is fully integrated, DBS will be transported from the 335 prevention of mother to child transmission of HIV sites.

As a result of the above challenges, Liberia started integrated use of the GeneXpert technology in 2015. This was designed with aim of filling the testing gaps of TB and HIV molecular tests and sustain epidemic preparedness and response capabilities for EVD and related outbreak testing. From online search of databases, we realized that our study is the first of its type to evaluate the integrated use of GeneXpert for TB, HIV viral load and EVD. It can be used as a model for using a laboratory platform for multiple disease diagnosis as well as active surveillance for epidemic preparedness. WHO also recommends collaboration and integration as a priority for those countries with currently operational multi-disease testing devices [18]. The objective of this study was to evaluate the impact of integrated use of GeneXpert testing for TB, HIV viral load and EVD and provide recommendations and strategies for scaling up of the services based on the findings of the study.

II. Method

a) Study setting

Liberia is a West Africa country with a population of about 4 million. This study was conducted in Liberia from December 2015 to March 2017(15 Months) from secondary data collected from 10 GeneXpert sites. All the sites with the GeneXpert machines installed by the MOH different programs and partners were included in the evaluation study. Redemption hospital, TB annex hospital, Phebe hospital, Liberian government hospital (Buchanan), Liberian government hospital (Tubman burg), John Kennedy (JFK) hospital, Ghanta Leprosy Rehabilitation hospital, Jackson F. Doe hospital, Tellewoyan hospital and J.J Dossen hospital were the sites where the evaluation study was conducted.

b) Study design

This was a retrospective study from the GeneXpert testing secondary data combined with observational field feasibility evaluation study of the impact of the integrated testing. A previously collected and reported GeneXpert testing data was used to evaluate the integrated use of GeneXpert platform for TB, HIV viral load and EVD testing. All the laboratory GeneXpert secondary data available since the machines were installed and started testing from December 2015 to March 2017 were analyzed. Data on the GeneXpert EVD, HIV viral load and MTB/RIF testing results, infrastructural and logistical requirements were collected. The study was conducted in Liberia from December 2015 to March 2017(15 Months) using secondary data collected from 10 GeneXpert sites. All the sites with the GeneXpert machines installed by the MOH different programs and partners were included in the evaluation study. Redemption hospital, TB annex hospital, Phebe hospital, Liberian Government Hospital

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(LGH)Buchanan, LGH (Tubman burg), John F. Kennedy Memorial Hospital (JFK hospital), Ganta Leprosy Rehabilitation hospital, Jackson F. Doe hospital, Tellewoyan hospital and J.J Dossen hospital were the sites where the evaluation study was conducted.

III. Results

The following findings were obtained from the programmatic intervention secondary data and feasibility field observations.

a) Field observation of the GeneXpert sites operation and coordination

To compliment the retrospective secondary analysis of the GeneXpert testing data of the three diseases, field observation on the installation of the GeneXpert machines, specimen collection, training, quality assurance and result reporting was included.

All the GeneXpert machines were installed in facilities by taking into consideration testing volumes, availability of uninterrupted power supply, reliable sample transport system, appropriate result reporting mechanism, existing laboratory network and human resource capacity. For site selection of instrument placement in the country, the MOH Laboratory team and partners considered epidemiological data on EVD, HIV viral load and TB, current EVD isolation facilities, HIV and TB Clinics and testing centers. To determine the suitability of the sites, the GeneXpert pre-installation checklists were used. In addition to the above-mentioned factors, GeneXpert instrument placement also took into consideration clinical and testing sites with high burden priority for EVD surveillance, HIV viral load and TB and clinical and testing sites that currently provide isolation facilities and/or care and treatment services for EVD, HIV viral load and/or TB. This will help to maximize patient outcomes and cost effectiveness. Before the installation of the GeneXpert machines at the health facilities, pre-installation assessment was done. Following the assessment, laboratory refurbishments were done. Four instruments were procured by the Global Fund for the TB program and eleven were available for EVD testing only. Altogether, 15 machines were used for this integration at ten facilities. Because of the high surveillance testing burden, Tapita hospital, Phebe hospital and Redemption hospital have each 4, 2 and 2 GeneXpert machines respectively. All instruments were fully integrated; allowing expanded testing by all sites as required.

All the laboratory staff involved in the integrated testing were trained for MTB/ RIF, HIV 1 viral load and EVD testing. The training for MTB/RIF and HIV 1 viral load was provided by CHAI Liberia. The training for EVD testing was conducted by FIND in collaboration with WHO and ACCEL. The training was conducted for five days. It covered practical skills about the operation of the GeneXpert system, principle of the test, interpretation of the assay, quality assurance, data management and troubleshooting. Pre and post-tests were also administered prior and after the training respectively.

Specimen collection for the three-diseases testing followed a standard procedure that ensured the safety of the staff at the GeneXpert site, avoided cross-contamination and minimized workload at the GeneXpert site laboratory. Sputum was processed at the TB sputum processing area and it was added into the cartridge at the site of processing. The cartridge was taken to the GeneXpert laboratory for analysis. ART nurses and laboratory technicians drew whole blood for HIV 1 viral load testing into a standard 4ml Ethylenediamine Tetra-acetic Acid (EDTA) tube. This specimen was taken to the GeneXpert laboratory and centrifuged. From the centrifuged specimen, 1 ml plasma sample was transferred to the HIV 1 viral load cartridge. For the EVD testing, the EDTA whole blood EVD specimens were inactivated at the collection site isolation unit. The inactivated specimen was taken to the GeneXpert laboratory. Processing of this inactivated specimen in the laboratory is considered safe and wearing full personal equipment is not required. An aliquot of the inactivated blood sample was then pipetted into the GeneXpert EVD cartridge and tested as per Cepheid's manufacturer instruction.

As part of ensuring the quality assurance of the integrated testing, job aids and standard operating procedures were developed. Besides temperature monitoring check list of the GeneXpert room as well as the refrigerators were also developed. A supervision checklist, result recording registers and instrument maintenance logs were used to regularly monitor the GeneXpert sites for addressing instrument failure, troubleshooting support and monitoring of testing error rates. The GeneXpert cartridge is also provided with sample processing control and probe check internal controls which monitor the adequacy of the specimen and the presence of PCR inhibitors respectively.

b) GeneXpert assay secondary data results

A total of 706 HIV 1 viral load, 3695 MTB/RIF and 2309 EVD GeneXpert tests were conducted since the start of the integrated testing in December 2015 to March 2017 (Table 1). This makes the total number of tests conducted for the three diseases 6710. These tests were conducted at the 10 GeneXpert sites located in 8 of the 15 counties in Liberia (Fig 1). The Turn Around Time TAT for the three diseases was one day. Because of the screening and isolation units that were established in Phebe and Redemption hospitals during the EVD outbreak, the two hospitals effectively used the GeneXpert machines for TB, HIV viral load and EVD.

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Table 1: Integrated GeneXpert testing for HIV viral load, EVD and MTB/RIF

GeneXpert facility	Number of HIV 1 Viral load tests conducted	Number of MTB/RIF tests conducted	Number of EVD tests	Total number of tests conducted
Redemption Hospital	427	556	217	1200
TB Annex Hospital	45	2208	0	2253
Phebe Hospital	19	277	2091	2387
LGH, Buchanan	20	247	0	267
JFK Hospital	145	0	1	146
LGH, Tubman burg	0	25	0	25
Ghanta Rehab Hospital	0	169	0	169
Jackson F. Doe Hospital	22	82	0	110
Tellewoyan hospital	8	40	0	48
J.J.Dossen hospital	20	91	0	91
Total tests conducted	706	3695	2309	6710



Figure 1: Location of the GeneXpert machines for the integrated testing for HIV 1 viral load, MTB/RIF and EVD

1. HIV 1 GeneXpert viral load testing results

A total of 706 HIV1 viral load tests were conducted from December 2015 to March 2017. The viral load tests have been conducted in five major hospitals where the highest number of HIV patients were enrolled for care and treatment. The hospitals included JFK, Redemption, Jackson F.Doe, J.J Dossen and Liberian Government hospital (LGH) in Buchanan (Table 2).

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Table 2: HIV 1 viral load tests conducted using GeneXpert (December 2015 to March 2017)

GeneXpert testing facilities	HIV 1 Not detected	Invalid result	No result	Total HIV Viral load tests	Viral load <1000 copies/ml	Viral load >1000 copies/ml	% HIV Viral suppression
Redemption Hospital	88	4	5	427	137 (33%)	186 (67%)	33%
TB Annex Hospital	5	1	1	45	9 (21%)	25 (79%	21%
Phebe Hospital	2	0	0	19	6 (32%)	11 (68%)	32%
LGH, Buchanan	2	0	0	20	13 (80%)	4 (20%)	80%
JFK Hospital	20	0	0	145	31 (21%)	96 (79%)	21%
Jackson F. Doe Hospital	3	2	0	22	1(5%)	16 (95%)	5%

For patients who are on ART, their viral load will decline and become less than 1000 copies/ml if they are responding to ART. In this study, the viral load suppression rate among viral load tested individuals was very low (Fig 2). This may be attributed to treatment interruption or ARV drug resistance.

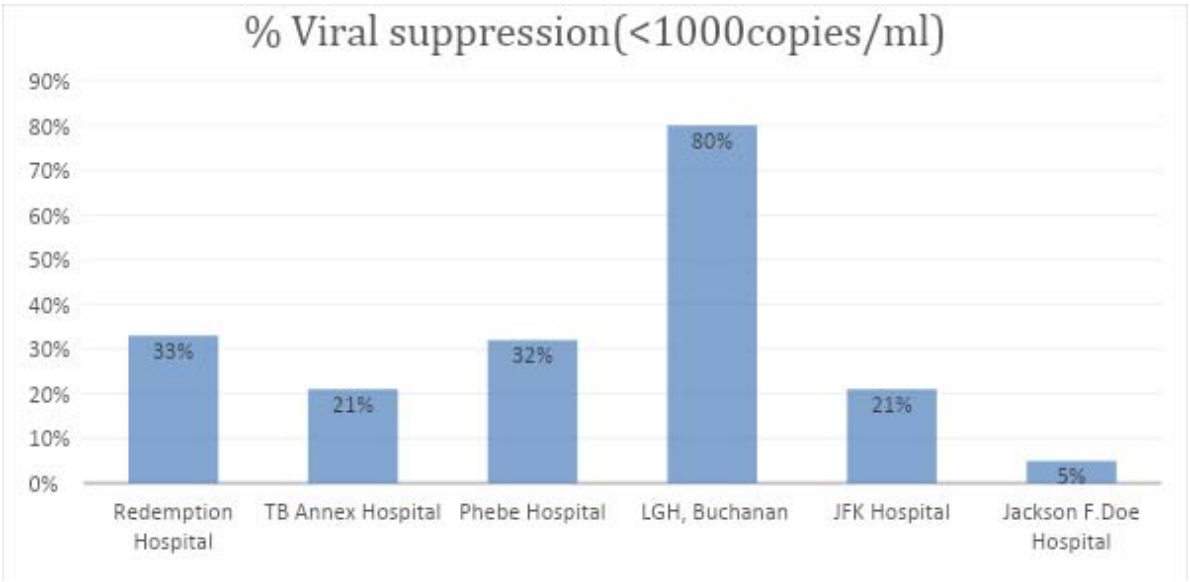


Figure 2: Percentage (%) of viral suppression

2. GeneXpert MTB/RIF testing results

Out of the ten sites with integrated testing, only the four site machines were procured for MTB/RIF by the NLTCP of Liberia. The number of MTB/RIF tests conducted from December 2015 to March 2017 is 3695. The number of RIF resistant MTB detected was high in TB Annex hospital and Redemption hospital. Phebe hospital showed the highest error rate followed by J.J Dosen hospital (Table 3).

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Table 3: MTB/RIF tests conducted on the integrated GeneXpert (December 2016 to March 2017)

Facility	MTB not detected	MTB detected/RIF not detected	MTB detected & Rif resistant	MTB detected/Rif indeterminate	Error	No result	Invalid	MTB/RIF Total tests
Redemption Hospital	357	155	15	7	5	13	4	556
TB Annex Hospital	689	326	72	16	9	0	12	1124
Phebe Hospital	191	65	2	0	15	2	2	227
LGH, Buchanan	109	106	3	3	3	22	1	247
JFK Hospital	0	0	0	0	0	0	0	0
LGH, Tubmanburg	14	6	0	0	5	0	0	25
Ganta Rehab Hospital	81	81	2	0	2	12	1	169
Jackson F. Doe Hospital	68	10	1	3	0	0	0	82
Telewoyan Hospital	0	0	0	0	0	0	0	0
J.J.Dosen Hospital	55	27	1	1	7	0	0	91

The Liberian government hospital in Buchanan and the Ganta rehabilitation center recorded 51% MTB positivity rate. The MTB/RIF test was not started in three hospitals. The positivity rate of MTB in Redemption hospital and TB Annex hospital were 33% and 36% respectively (Fig 3)

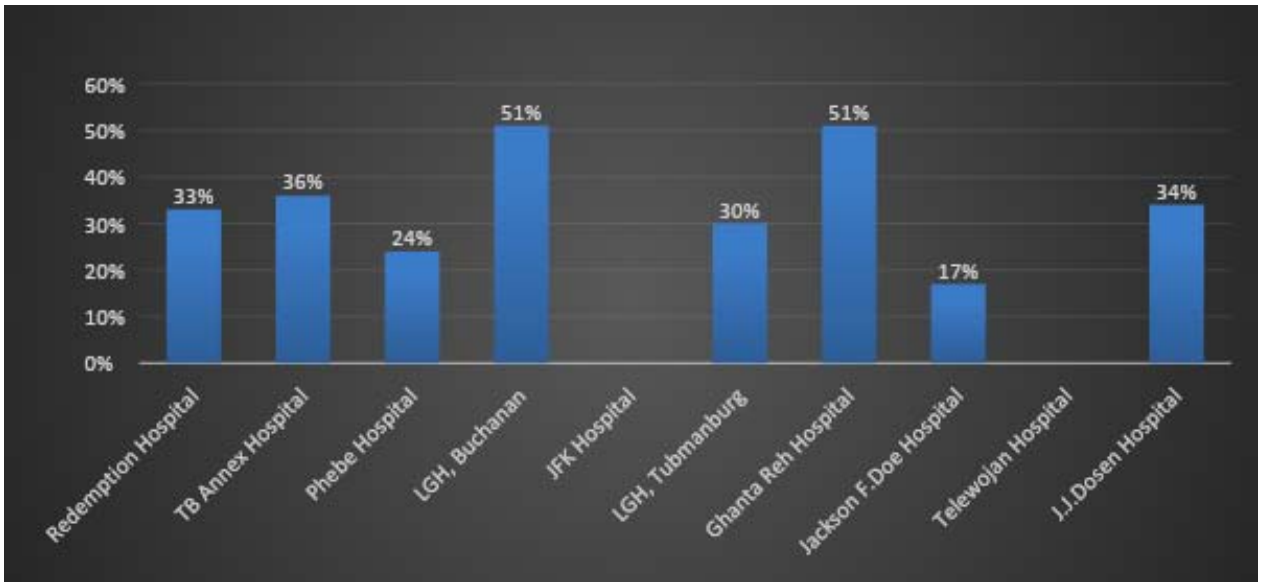


Figure 3: MTB positivity rate

The GeneXpert utilization rate was 38% for TB annex hospital. Although high number of TB suspected cases in the country and the high number of GeneXpert MTB/RIF cartridges available at the central stores, the GeneXpert machines were underutilized (Fig 4).

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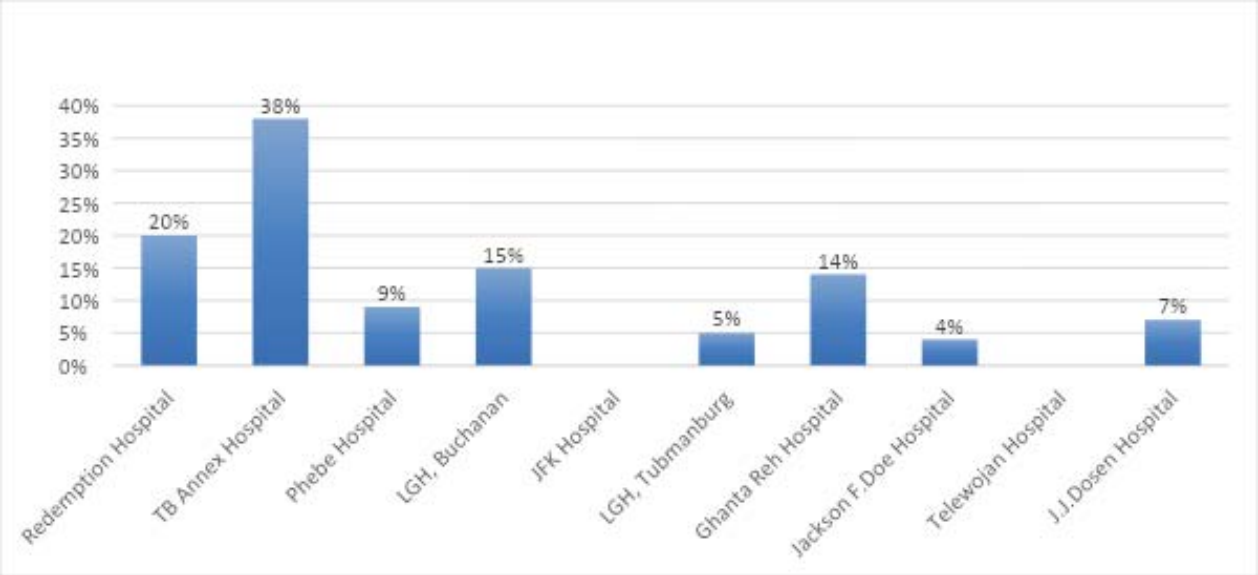


Figure 4: GeneXpert utilization rate for MTB/RIF

The above utilization rate was calculated with the assumption of 3 runs per day per machine and consideration of 20 working days per month. The highest utilization rate is for TB annex hospital which is only 38 % and the utilization rate in other facilities is as low as 4% and even in some facilities the MTB/RIF test was not started despite the fact that training was conducted and the cartridges were available in the facilities (Fig 4). The utilization rate for HIV viral load was by far lower than the utilization rate of MTB/RIF. The HIV viral load utilization rate of Redemption hospital, John F. Kennedy memorial hospital and TB Annex hospital was 15%, 7% and 2% respectively. The HIV viral load utilization rate for the other facilities was 1%.

IV. Discussion

The integrated testing of HIV1 Viral load, MTB/RIF and EVD using the GeneXpert platform has played a significant role in Liberia. Even though the first GeneXpert for MTB/RIF was installed in 2013, It was underutilized, and the MTB/RIF was interrupted. The reasons for the interruption were the expiration of the MTB/RIF cartridges at the end of 2013 and the EVD outbreak of 2014 in Liberia. As result of the integrated use of the GeneXpert machines, HIV viral load testing was re-initiated in December 2015 after one year of interruption by the EVD outbreak. The WHO Liberia office and ACCEL procured GeneXpert machines for EVD surveillance in 2015. It was few weeks after the EVD assay was prequalified by WHO.

Liberia diagnosed its first cases of Ebola in March 2014. Liberia was declared free of Ebola for the first time in May 2015. However, the country faced another outbreak in June 2015, was declared free of transmission on September 2015, experienced three more cases in November 2015 and was again declared Ebola-free on January 2016.The magnitude as well as the frequent re-emergence of the EVD outbreak indicated the need for building sustained diagnostics to support surveillance and emergency preparedness. This can be achieved by building the capacity of clinical laboratory in such a way to shift in addressing any occurrence or re-occurrence of epidemic as well as emerging diseases [17]. EVD machines were installed in some EVD isolation facilities in 2015 at the time when the outbreak was declining. No positive EVD result was detected from the GeneXpert machines and they have been in use for surveillance and readiness in case of future re-occurrence. The MOH of Liberia NLTCP, NACP and CHAI took this as a golden opportunity to use the EVD machines in an integrated way to test MTB/RIF and HIV viral load. The GeneXpert machines were procured by NLTCP have also been used for EVD and viral load testing. It was with this context that the three tests were integrated. 2309 EVD tests were conducted since the start of the integration in December 2015 to March 2017. Liberia was declared free of EVD during this interval and there was no positive EVD result. The integrated approach helped in active surveillance. In all the sites where the three-disease testing was integrated, the international partners working in laboratory strengthening trained enough local manpower who can run EVD molecular tests in their absence. Running the GeneXpert by Liberian nationals makes the preparedness and response to any future outbreak very sustainable. The integrated use of GeneXpert platform at EVD isolation facilities has strengthened preparedness and early response capabilities for future EVD outbreaks in Liberia [17].

According to the 2013 WHO integrated guidelines, HIV viral load testing for patients on ART is crucial for monitoring treatment response [19]. Despite this, Liberia has not successfully initiated a steady viral

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load testing until the Ebola outbreak in 2014. Viral load testing was interrupted during the EVD in 2014 due to the HIV molecular laboratory been converted to test EVD. With technical support from CHAI, reagent support from WHO, the Global Fund and the National Diagnostics Unit Viral load test was started successfully at Redemption hospital, TB annex hospital, JFK hospital, Phebe hospital, Jackson F. Doe and the Liberian Government hospital in Grand Basa on four- modules GeneXpert machines procured for MTB/RIF and EVD testing. The WHO guidelines for integrating HIV and TB services in Liberia was implemented before the EVD outbreak [20]. The NLTCP, in collaboration with the NACP of Liberia, has- integrated TB/HIV services in 24.9% of the 551 functional health facilities in the country [21]. The efforts to initiate viral load testing at the National Reference Laboratory and the St. Joseph Catholic hospital was interrupted by the EVD outbreak. After the first EVD outbreak, all the HIV 1 Viral load reagents and consumables were expired. The PCR machine at the Catholic hospital was damaged during the outbreak. The HIV viral load test was interrupted for more than one year. The HIV real time PCR machines, reagents and consumables requested by NACP to be procured by the Global Fund to restore the service were delayed for more than six months. The only opportunity to restore the HIV viral load testing in Liberia was to use the MTB/RIF and EVD GeneXpert machines in an integrated manner. The integrated approach helped the program to initiate viral load for treatment monitoring.

In 2014, the Joint United Nations Program on HIV/AIDS and partners launched the 90–90–90 targets which refer to the pathway by which 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy to achieve 90% viral suppression of those treated by 2020 [22].

The GeneXpert utilization rate of HIV viral load was low in almost all of the GeneXpert sites. The poor specimen referral linkage from the 55 sites which offer ART services in Liberia to the GeneXpert testing sites was one of the reasons. The low HIV viral load request by the ART clinicians was the other reason for the underutilization of the GeneXpert viral load test. A study conducted on multi-disease GeneXpert testing in Zimbabwe demonstrated higher utilization of the HIV viral load cartridges than our findings [8]. Our study findings also indicated a very low viral load suppression percentage that could have been resulted from poor adherence to treatment.

The integrated approach is also helpful for the NLTCP of Liberia as MTB/RIF tests were conducted at facilities where the GeneXpert was installed for EVD testing. The NLTCP procured excess cartridges for the four machines in the entire country. The expiration dates of the cartridges were very short and the integration helped the TB program to utilize the cartridges before they expired. A result of this integrated use, 3695 MTB/RIF tests were conducted during the study period. The utilization rate of MTB/RIF is very low in Liberia compared to the utilization rate of the 21-high burden countries [23].

The current algorism of the NLTCP of Liberia is using the GeneXpert MTB/RIF as an initial diagnostic test in individuals suspected of MDR i.e. treatment failure cases only. The NLTCP should revise the algorithm to increase the utilization of the GeneXpert MTB/RIF cartridges and consider replacing AFB microscopy with GeneXpert for case finding in high burden areas. Our study findings also indicated a high positivity rate for MTB/RIF compared to the positivity rate of the sputum microscopy at each facility. As far as resources are available, using the MTB/RIF assay for all patients except for follow up patients can increase the detection rate and is crucial in prevention of the spread of the disease as TB suspects are diagnosed earlier. The 2013 WHO guidelines on MTB/RIF GeneXpert included a conditional recommendation for GeneXpert MTB/RIF as the initial diagnostic test in all adults with suspected TB, acknowledging resource implications [11]. Besides, the NLTCP has to regularly sensitize clinicians to increase the utilization of GeneXpert and to strengthen sputum sample transportation system from peripheral to the GeneXpert sites.

During the implementation of the integrated use of the GeneXpert platform, the GeneXpert system has two basic internal controls which monitor the instrument, cartridge content and system contents for each test conducted. The sample adequacy control ensures that sufficient sample is added to the cartridge in a detectable amount. The sample processing control checks for PCR inhibition caused by cross contamination during specimen preparation in the laboratory [24]. Despite the above-mentioned controls provided with in the cartridges, there was no External Quality Assessment (EQA) proficiency panel provided from any source.

The testing turnaround time obtained from the GeneXpert site laboratories registers indicated patient test reporting time in hours compared to the conventional tests which provided results in days. The GeneXpert technology provides result in an average of 2 hours and allows for single specimen testing to overcome potential delays of batching compared to the conventional molecular testing.

An estimated 26,313 adults and 2,339 children were living with HIV in 2015 respectively. The population of Liberia is about 4,000,000. The prevalence of HIV in the general population aged 15-49 is 2.1%. Out of the estimated 26,313 adults and 2,339 children who were living with HIV in 2015, only 8000 were enrolled on ART [6]. Considering the burden of TB, a total of 7,119 patients in Liberia were diagnosed with TB in 2016 including 857 children. The estimated incidence and the

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estimated prevalence of TB in Liberia for the year 2016 was 300 per 100,000 population and 490 per 100,000 population respectively [13]. With the current national testing algorism of the NLTCP and NACP, strategic placement of one 4 module GeneXpert machines for the integrated tests of the three diseases in the six counties where GeneXpert testing machine is not installed is very helpful. Together with the existing 15 GeneXpert machines, the testing need of the three diseases can be met. These took into consideration the weak specimen referral system, the bad road condition and the lack of infrastructure in the health facilities in Liberia. Any national algorism changes in line with WHO recommendation can be accommodated by these strategic placements of the GeneXpert machines.

Challenges of the integration

- The procurement of the GeneXpert supplies and cartridges was not well coordinated. Proper forecasting and quantification of cartridges, calibrators and other accessors must be conducted on regular basis.
- The short expiration date of EVD and HIV viral load cartridges resulted in shortage of cartridges and interruption of testing service.
- HIV 2 is known to be prevalent in West African region. GeneXpert assay for detection of HIV2 has not been developed yet.
- The was no strong specimen referral system for HIV viral load and MTB/RIF.
- Regular calibration of the machines was one of the challenges as there was no in-country authorized service provider.
- Failure of air conditioners in some facilities contributed to high error rates.
- There was underutilization of the GeneXpert plat form in some sites. This was due the weak specimen referral system and the limited number of isolation units to screen and take EVD specimen.
- There was lack of coordination of the three programs as there was no focal person designated to coordinate the integration at facility and at national level.
- Data connectivity has not been implemented yet.

V. Recommendations

Integrated use of the GeneXpert technology will improve patient outcomes if it is implemented within the context of strong and well-coordinated programs and systems of the three diseases. The following recommendations are provided based on the findings of the study.

- Guidelines, policy and strategy for scaling up the GeneXpert technology to support integrated diagnostics for EVD, HIV and TB should be developed. This helps to coordinate activities and to designate the role and responsibilities. This should include decentralized testing throughout the country and building local capacity to address epidemics.
- Strong collaboration should be developed between the NLTCP of Liberia, the NACP of Liberia and the National Public Health Institute of Liberia in resource mobilization and coordination of the integrated testing.
- Training should be provided to clinicians to use the proper national algorism for each disease. This will ensure effective utilization of the cartridges, minimize wastes and expiry and maximize/improve patient outcome.
- Proper monitoring and evaluation of the integrated testing services regularly using appropriate indicators should be considered.
- The role and responsibility of implementing partners for each disease testing should be defined and coordinated by MOH to ensure sustainability in the absence of partners.
- Master trainers and trainers of trainees should be identified, trained and availed.
- Master-list of instruments should be compiled and updated regularly to keep track of all instruments in-country, including serial numbers, installation dates, supporting partners, calibration dates, maintenance and trained users.
- Training modules should be defined and approved by MOH, including pre and post-training assessment of competencies as well as mentorship with monitoring and evaluation plan.
- Establishment hotline system for remote support and implementing connectivity tools like the GxAlert should be considered.
- Regular quantification and forecasting of cartridges based on history of consumption and/or epidemiological data should be conducted.
- EQA panels were not available for proficiency testing for GeneXpert EVD, Viral load and MTB/RIF. The development of low-cost panels should be considered.
- Enhanced adherence counselling should be provided to patients with viral load higher than 1000copies/ml.

VI. Conclusions

Integrated use of the GeneXpert platform significantly improved the testing services for HIV viral load and MTB/RIF testing. It increased access to viral load testing for monitoring treatment failure. It also helped to utilize the EVD GeneXpert machines and sustain the epidemic preparedness and response. Despite the integrated approach, the utilization rate of the GeneXpert machines in the country is very low. There is lack of coordination of logistics, weak specimen referral system, expiry and stockout problems and lack

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of connectivity. The high cost of the cartridges to support continuous testing is a challenge. The three disease programs and partners should coordinate and effectively implement the integrated use and scale up the services. Each step of the integration should be monitored regularly. This is crucial in sustaining the EVD surveillance testing capacity in Liberia and help the TB and HIV programs in meeting the 90-90-90 targets for both diseases by 2030. The significant reduction in turnaround time is a critical advantage in the GeneXpert usage.

Declaration

Ethics approval and consent to participate

Permission to use the existing data from programs and GeneXpert sites database was provided by the NACP of Liberia, the National Leprosy and Tuberculosis program (NLTCP) of Liberia as well as the health facilities where the GeneXpert machines are used for multiple testing (S1 Text).

Consent for publication

Not Applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on request.

Competing interests

The authors declare that they have no conflict of interest which may have inappropriately influenced them in writing this article.

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Wash Out "Corona Virus" from "Throat

By C K Jayaram

Introduction- It is widely confirmed in all media that Washing hands with soap destroys completely "corona Virus". If the above is true, then we have to examine if any device can be devised that can completely and efficiently wash the Throat areas with soap water, to rid the virus.

It is widely advertised that the Corona virus stays in the Throat for 3 to 4 days before it enters the Lungs after which there is no going back.

In the above context I have drawn sketch of a device similar to the cluster of tubes inserted in the throat through the mouth of patients undergoing operations.

The mechanism has following different pipes (Total 4 Nos.) which are embedded one inside the other concentrically, as shown in the Sketch attached.

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

WASHOUTCORONAVIRUSFROMTHROAT

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Wash Out "Corona Virus" from "Throat

C K Jayaram

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The mechanism has following different pipes (Total 4 Nos.) which are embedded one inside the other concentrically, as shown in the Sketch attached.

The functions of these Tubes individually are as below:-

Tube (A): This is the Camera tube which enables insertion of the mechanism smoothly and to position the mechanism at the appropriate locations.

Tube (B): This pipe is inserted concentrically and serves the purpose of free breathing of the patient with feeding of normal air or oxygen.

Tube (C): This tube is having an expandable bulb attachment at the end which when inflated acquires the desired dimensions and hold tightly against the Wall of the Throat and act as a sealant to ensure that the Soap water used does not seep into the Stomach or the Lungs. It may not be fatal even if the Soap water seeps a bit. This tube while acting as a sealant of the throat, down beyond the operational area, also acts a scraper while withdrawing from the Patient's Mouth/ Throat at the end of the operation. This will ensure complete (100%) removal of residual soap water remaining on the walls of the throat left over if any in the operational zone. This pipe is of expandable type, operated and dimensions controlled by pumping of air from a Pump.

Tube (D): This is also concentrically inserted and serves the purpose of cleaning the walls of the Throat with Soap |Water, Rinsing, and sucking out the soap water used and re spraying of fresh soap water for repeated cleaning and rinsing operation of the throat walls this Pipe is also expandable type and operated Air of liquid for expansion. This has wiping bulb at the ends circumferentially, and the tube can reciprocate its movement vertically up and down the throat, simultaneously spraying medicated soap water on the the walls of the throat, moving up and down cleaning the surface, rinsing and sucking out the washed soap water remains.

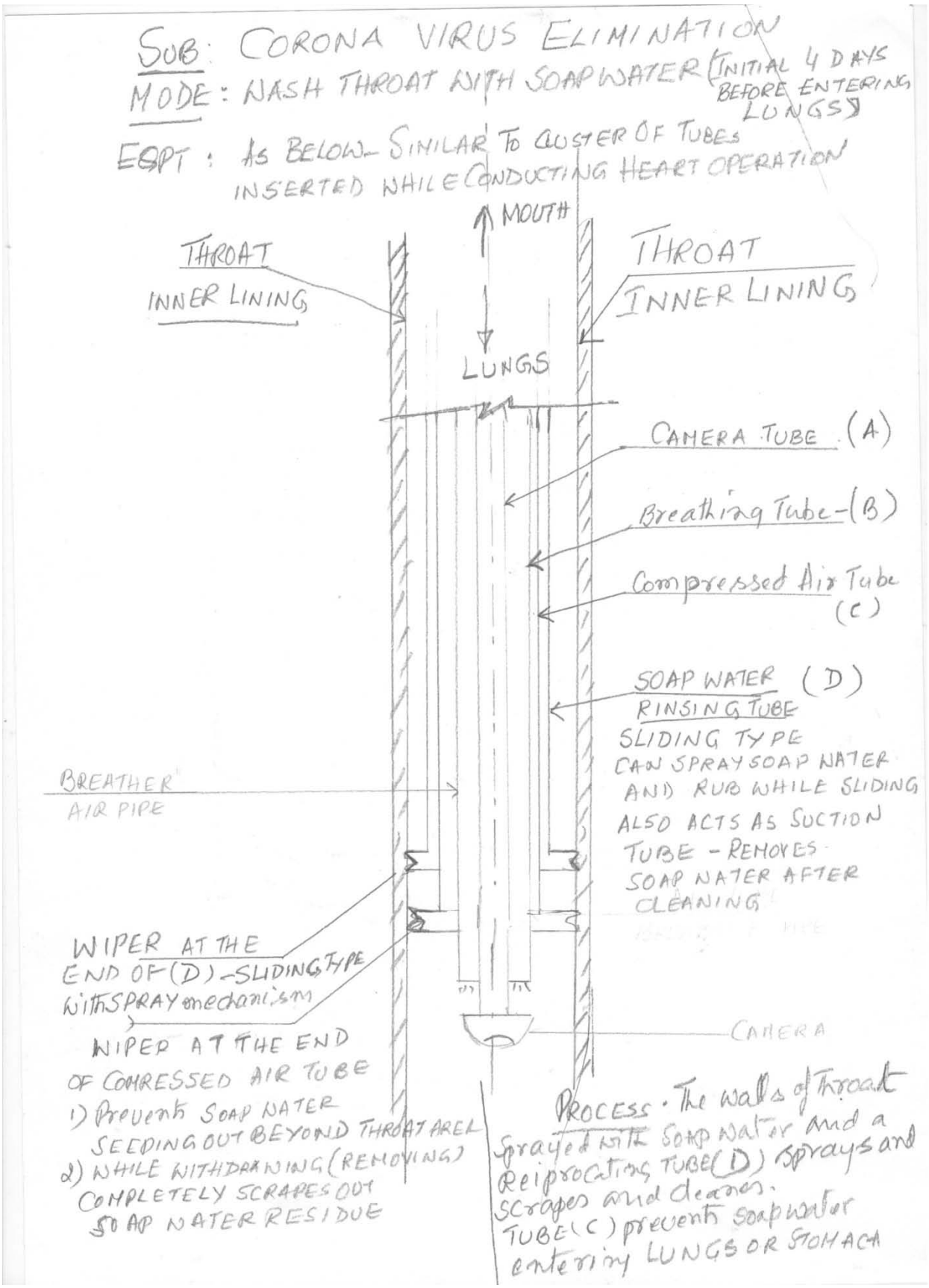
I request this may be examined by experts for incorporation if there is any possibility with this mechanism suggested to vipe out Corona virus.

Thanking you, your's sincerely Jayaram.

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

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Sketch Below:



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Additive Effect of Oral Tetradecanoic Acid to Tamsulosin and Finasteride in a Benign Prostatic Hyperplasia Rat Model

By Anup Patil, Dr. R. C. Doijad, Dr. P. V. Salve & A. A. Koparde

Abstract- We investigated the benefit of the tetradecanoic acid combined with tamsulosin and finasteride, in a benign prostatic hyperplasia (BPH) rat model. By bilateral orchiectomy under ketamine anesthesia Castration was performed. A rat model of BPH was established by daily intramuscular administration of testosterone propionate plus 17 alpha-estradiol for 8 weeks. For 4 weeks from week 6 to 9 post-surgery model rats were administered combinations of 20 mg/kg of tetradecanoic acid, 0.01 mg/kg tamsulosin and 1 mg/kg finasteride once daily by oral gavage. Body and genitourinary organ weights were recorded, serums were assayed for hormone concentrations, and tissues were subjected to histopathology Combined tetradecanoic acid, tamsulosin, and finasteride significantly decreased prostatic index, serum hormone levels, epithelial thickness, The 3-drug combination was more effective than any other combination or tetradecanoic acid alone. These results suggest that tetradecanoic acid addition to tamsulosin and finasteride may be beneficial for the treatment of BPH patients who do not respond to tamsulosin plus finasteride.

Keywords: *5alpha-reductase inhibitor, tetradecanoic acid, tamsulosin, finasteride.*

GJMR-F Classification: *NLMC Code: WJ 752*



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Additive Effect of Oral Tetradecanoic Acid to Tamsulosin and Finasteride in a Benign Prostatic Hyperplasia Rat Model

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Abstract- We investigated the benefit of the tetradecanoic acid combined with tamsulosin and finasteride, in a benign prostatic hyperplasia (BPH) rat model. By bilateral orchiectomy under ketamine anesthesia Castration was performed. A rat model of BPH was established by daily intramuscular administration of testosterone propionate plus 17 alpha-estradiol for 8 weeks. For 4 weeks from week 6 to 9 post-surgery model rats were administered combinations of 20 mg/kg of tetradecanoic acid, 0.01 mg/kg tamsulosin and 1 mg/kg finasteride once daily by oral gavage. Body and genitourinary organ weights were recorded, serums were assayed for hormone concentrations, and tissues were subjected to histopathology Combined tetradecanoic acid, tamsulosin, and finasteride significantly decreased prostatic index, serum hormone levels, epithelial thickness, The 3-drug combination was more effective than any other combination or tetradecanoic acid alone. These results suggest that tetradecanoic acid addition to tamsulosin and finasteride may be beneficial for the treatment of BPH patients who do not respond to tamsulosin plus finasteride.

Keywords: 5alpha-reductase inhibitor, tetradecanoic acid, tamsulosin, finasteride.

I. Introduction

Urinary urgency, slow stream, nocturia and increased daytime frequency various symptoms prostate enlargement.[1] Benign prostatic hyperplasia (BPH), also known as benign enlargement of the prostate, is a hormone and age-related disease characterized by histological changes in the prostate gland and variable enlargement of the prostate.[2] Negative effect on the quality of life of BPH patients considerable due to these symptoms. [3, 4] Although the pathogenesis of BPH is hormonal changes in an aging man.[5] Androgen stimulation, by dihydrotestosterone (DHT) that is a highly active metabolite of testosterone synthesized from the prostate 5 alpha- reductase enzyme responsible for development and growth of normal prostate.[6,7] Treatment options exist: alpha1-adrenergic receptor antagonists and 5 alpha-reductase inhibitors to reduce smooth muscle tone in the prostate and the bladder neck, and reduce prostate size simultaneously for patients with BPH.[8] Tamsulosin and finasteride have been the most popular medication but furthermore, these drugs induce undesirable side effects, including decreased libido, erectile dysfunction, dizziness, postural hypotension, asthenia, and occasional syncope prescribed for treating BPH.[9] McConnell et al[10] reported that only 64% of men receiving both therapies showed the reduced risk of clinical progression, defined as worsening of symptoms, acute urinary retention, incontinence and urinary tract infection.[11,12] Therefore, it is highly desirable to develop an alpha1-adrenergic antagonist or other medication that can selectively suppress the smooth muscle tone of lower urinary tract without vascular effects and decrease prostate volume without sexual dysfunction for the treatment of urinary outlet obstruction.[14] Recently oral administration of tetradecanoic acid (70 and 140 mg/kg) is used for prevention of BPH produced no clinical signs or adverse effects.[15] The purpose of this investigation was to evaluate that addition of oral tetradecanoic acid to conventional tamsulosin plus finasteride treatment can augment pharmacological efficacy in a BPH rat model.

II. Materials and Methods

a) Chemicals and reagents

Testosterone was purchased from Sigma-Aldrich. Finasteride and 17 alpha-estradiol were purchased from Sigma-Aldrich). Tamsulosin was donated by ILDONG Pharmaceutical Company (Seoul, Republic of Korea) All other chemicals were purchased from standard suppliers. Testosterone plus 17alpha-estradiol used in this study was dissolved in corn oil. tetradecanoic acid was dissolved in 10% Tween 20 buffer All animal procedures in this study were performed in accordance with the Guide for the Care and Use of CPCSEA.

b) Treatment of BPh rat model with tetradecanoic acid, tamsulosin and finasteride

A total of 42 male SD rats (250–300 g) were selected for this study. The 6 rats were incised above the pelvic region on the ventral side and then sutured without cutting off the testicles as a control group (CON ±Vehicle). The testicles of 36 male SD rats were removed under anesthesia with intraperitoneal ketamine (50 mg/kg;) and 2% xylazine hydrochloride (25 mg/kg;).

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The 6 castrated rats were intramuscularly administered corn oil (CAS+Vehicle). A week after castration, 30 rats were intramuscularly administered testosterone (3 mg/kg) plus 17β-estradiol (0.03 mg/kg) daily for 8 weeks to induce BPH. The 30 castrated BPH rats were then randomly assigned to 5 experimental groups: Positive control group (BPH+Vehicle), tetradecanoic acid-treated (BP+T), tetradecanoic acid and tamsulosin-treated (BPH+TT), tetradecanoic acid and finasteride-treated (BPH+TF) and tetradecanoic acid tamsulosin and finasteride-treated (BPH+TTF). Treatment groups received the indicated combination of tetradecanoic acid (20 mg/kg), tamsulosin (0.01 mg/kg) and/or finasteride (1 mg/kg) once daily for 4 weeks from week 6 to 9 post-surgery. The volumes of administration were 6 mL/kg for oral administration and 0.7 mL/kg for intramuscular injection, respectively. The volumes were calculated based on recent weights.

c) *Sample collection*

Blood was obtained from the abdominal vein. Organs such as the prostate, bladder, penis and seminal vesicles were surgically removed. Prostate volume was measured and the prostatic index was calculated as prostate volume/body weight X100.

i. *Measurement of hormone levels in the serum*

Serum levels of DHT, testosterone, were measured using commercial kits. All protocols were performed according to the manufacturer's instructions.

ii. *Histopathological examination*

Fixed prostate tissues embedded in paraffin wax were cut into 4 cm thick sections and stained with hematoxylin (Sigma- Aldrich) and eosin (Sigma-Aldrich). The sections were mounted and cover-slipped using mounting medium and then examined under a microscope.

iii. *Statistical evaluation*

All analyses were performed using SPSS version 12.0. Values are expressed as mean ± SD. Differences among treatment group means were tested by analysis of variance and post-hoc Duncan's multiple range tests. A *P*-value > 0.05 was considered statistically significant for all tests.

III. Results

a) *Effects of tetradecanoic acid, tamsulosin and finasteride combinations on body and genitourinary organ weights*

Body weight at 1 week post-castration did not differ among the groups (Table 1). However, body weight at 9 weeks post-castration was significantly lower in the disease control group compared to the castration group (CAS±Vehicle) and the sham-operated control group (CON±Vehicle). The absolute prostate volume and prostatic index were significantly lower in the BPH±L group than the disease control group and lower still in the group receiving all three drugs (BPH±LTF group).

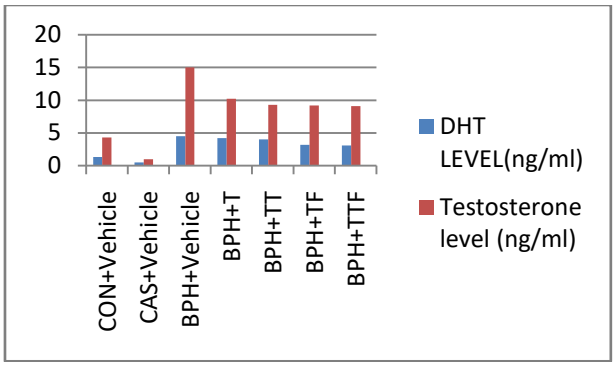
Table 1: Changes in weights of body and genitourinary organs

Group	Prostate volumes		Penis (g)	Seminal vesicle (g)	Bladder (g)	Body weights (g)	
	Absolute volume (g)	Prostatic index				1 week	9 week
CON+Vehicle	0.78±0.25^{d}	0.22±0.06^{c}	0.44±0.08^{c,d}	0.42±0.07^{d}	0.17±0.04^{c}	329.33±24.73	423.10±13.40^{a}
Cas+Vehicle	0.14±0.04^{e}	0.03±0.01^{d}	0.25±0.07^{e}	0.14±0.06^{e}	0.08±0.02^{b,c}	331.57±13.99	415.05±06.74^{a}
BPH+Vehicle	1.90±0.30^{a}	0.58±0.14^{a}	0.45±0.05^{a}	0.76±0.14^{a}	0.24±0.06^{a}	336.00±08.53	349.45±12.57^{b}
BPH+T	1.41±0.08^{b}	0.42±0.03^{b}	0.54±0.07^{a,b}	0.67±0.08^{b}	0.21±0.07^{a,b}	347.20±04.55	354.01±09.74^{b}
BPH+TT	1.45±0.13^{b}	0.40±0.05^{b}	0.32±0.08^{b,c}	0.66±0.10^{b,c}	0.17±0.09^{a,b}	339.00±12.49	348.55±08.53^{b}
BPH+TF	1.37±0.11^{b}	0.38±0.02^{b}	0.42±0.05^{c,d}	0.58±0.13^{b,c}	0.15±0.04^{b,c}	339.80±22.53	352.31±10.12^{b}
BPH+TTF	1.13±0.12^{c}	0.33±0.05^{b}	0.43±0.12^{d}	0.57±0.10^{c}	0.15±0.03^{b,c}	330.83±23.58	355.78±23.74^{b}

Notes: Values with different superscript alphabets in the same row are significantly different (P < 0.05) by one-way analysis of variance and the Duncan's multiple range tests. Abbreviations: BPH, benign prostatic hyperplasia; BPH+Vehicle, Positive control; BPh+ T, tetradecanoic acid (20 mg/kg); BPh+ T T, tetradecanoic acid and tamsulosin (0.01 mg/kg); BPh+TF, tetradecanoic acid and finasteride (1 mg/kg); BPH+TTF, tetradecanoic acid, tamsulosin, and finasteride; CAS+Vehicle, castration; CON+Vehicle, control.

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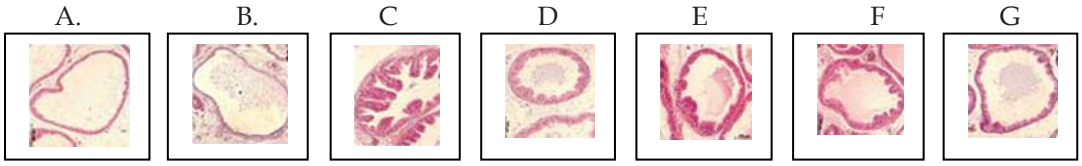
Effects of tetradecanoic acid, tamsulosin and finasteride combinations on serum hormones.



Serum DHT, testosterone, free testosterone, and estradiol levels are shown in Figure 1. Serum DHT was markedly higher in the disease control group (4.70±0.19 ng/mL) than the CON±Vehicle group (Figure 1A). However, DHT levels were significantly lower in the BPH±L group (4.06□0.59 ng/mL) and lower still in the BPH±LTF group (2.97±0.55 ng/mL) compared with the disease control group. The disease control group also exhibited significantly increased serum testosterone (15.66±2.79 ng/mL) compared with the CON±Vehicle group (3.31±1.05 ng/mL; Figure 1B). In contrast, serum testosterone levels were significantly lower in the BPH±L and BPH±LTF groups compared with the disease control group.

b) Effects of tetradecanoic acid, tamsulosin, and finasteride combinations on prostatic epithelial hyperplasia

Histopathological studies results revels the beneficial effects of tetradecanoic acid tamsulosin and finasteride on epithelial hyperplasia. Maximum hyperplasic cell are observed in C slide (BPH+ vehicle) there was maximum hyperplasia maximum proliferation of cells. Group D, E, F, G maximum protection on histoarcheture was observed.



A: CAS+Vehicle, castration, B: CON+Vehicle, control, C: BPH+Vehicle, Positive control; D: BPH+ T, tetradecanoic acid (20 mg/kg); E: BPH+ T T, tetradecanoic acid and tamsulosin (0.01 mg/kg); F: BPH+TF, tetradecanoic acid and finasteride (1 mg/kg); G: BPH+TTF, tetradecanoic acid, tamsulosin, and finasteride.

IV. Discussion

DHT is an important factor in BPH pathogenesis as it is the androgen primarily responsible for prostate growth.[16] DHT stimulates the transcription of growth factors that are mitogenic for prostate epithelial and stromal cells.[7] Finasteride, a type II 5+reductase inhibitor, that reduces epithelial cell size and the proliferative activity of DHT, is used for treating human BPH.[17] Surgical treatments, such as transurethral resection of the prostate, are performed most widely as the second option for patients who do not respond completely to combined finasteride plus tamsulosin therapy.[18] In the present study, LTF treatment reduced BPH- dependent DHT elevation to a greater extent than tetradecanoic acid alone. These results indicate that combined administration of tetradecanoic acid, tamsulosin, and finasteride have additive or synergistic anti-proliferative effects, possibly by interfering with androgen signaling. The prostatic index is used as a clinical marker of BPH development[5] and prostatic index is higher in animal models of BPH[19]. In the present study, oral administration of tetradecanoic acid, with tamsulosin and finasteride significantly reduced the prostatic index, serum hormone levels, in a rat model of BPH. Finasteride and other agents commonly used to treat BPH clinically also decrease the prostatic index.[20] The rat model established in this study exhibited an increased prostatic index compared with castrated rats, while tetradecanoic acid alone (BPH+T group) induced a reduction in prostatic index compared with the disease control group. Justulin et al [21]. These results indicate that combined administration of tetradecanoic acid, tamsulosin, and finasteride attenuated prostatic enlargement induced by testosterone plus 17+estradiol to a greater degree than tetradecanoic acid alone (or tetradecanoic acid with either tamsulosin or finasteride). BPH involves the proliferation of prostate epithelial and stromal cells, resulting in increased prostate weight and volume.[22] The prostate is connected to the urethra by

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fascia and a series of ducts in rats.[23] When the prostate is sufficiently large, it can physically compress the urethra, resulting in partial or sometimes complete obstruction.[24] The disease control group showed marked epithelial hyperplasia compared with the CON+Vehicle group, which was only mild in BPH rats treated with tetradecanoic acid alone or a combination of tetradecanoic acid, tamsulosin, and finasteride.

V. Conclusion

Combined tetradecanoic acid, tamsulosin, and finasteride significantly decreased prostatic index, serum hormone levels, epithelial thickness, The 3-drug combination was more effective than any other combination or tetradecanoic acid alone. These results suggest that tetradecanoic acid addition to tamsulosin and finasteride may be beneficial for the treatment of BPH patients who do not respond to tamsulosin plus finasteride.

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3. Final approval of the version of the paper to be published.

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Acknowledgments

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

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

Manuscript Style Instruction (Optional)

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

Structure and Format of Manuscript

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

A research paper must include:

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

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

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

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

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Format Structure

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All manuscripts submitted to Global Journals should include:

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The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

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

Abstract

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

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

Keywords

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

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

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

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

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

Numerical Methods

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

Abbreviations

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

Formulas and equations

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

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

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

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

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Tips for writing a good quality Medical Research Paper

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

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

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

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

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

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

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

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

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

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

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

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

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

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

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

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

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

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

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

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

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

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

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

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

The discussion section:

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

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

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To make a paper clear: Adhere to recommended page limits.



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

Title page:

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

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

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

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

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

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



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Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

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

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

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

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

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

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

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Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

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

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Topics	Grades		
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References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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