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World Evidence From Eastern

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Health Services Nursing Actions

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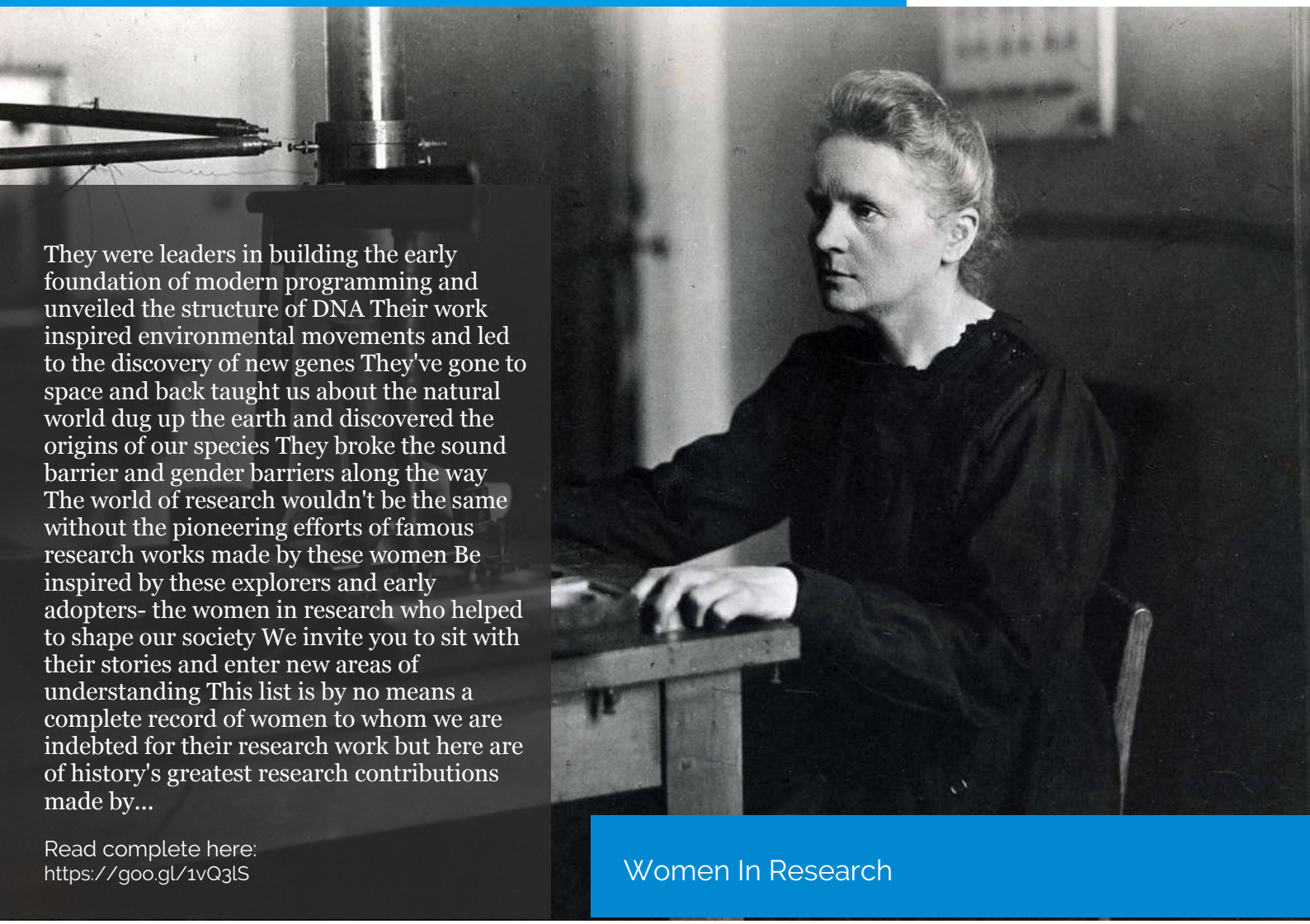

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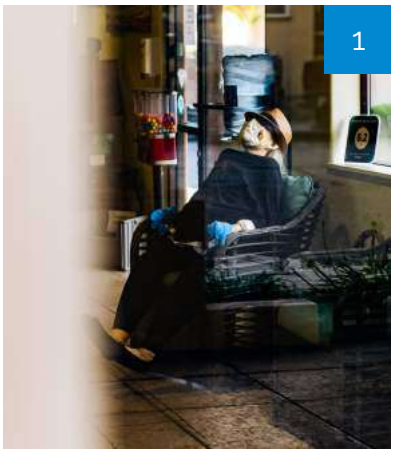

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Jianlie Zhou & Xingquan Zhang

"Vitamin D Today" website & University of California

ABSTRACT

Corona Virus Disease 2019 (COVID-19) is a global pandemic. Vitamin D with VDR may reduce risk of COVID-19 by up-regulating intercellular adhesion, down-regulating ACE2 level and immune-modulating effects. There are many evidences of Vitamin D against COVID-19 from the epidemiological, Clinical and meta-analysis findings. The further study will focused on the correlation between vitamin D supplementation and prevention and treatment of COVID-19 disease.

Keywords: covid-19, vitamin d, prevent, treatment.

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Vitamin D May Reduce Risk of Covid-19: A Review

Jianlie Zhou[α] & Xingquan Zhang[σ]

ABSTRACT

Corona Virus Disease 2019 (COVID-19) is a global pandemic. Vitamin D with VDR may reduce risk of COVID-19 by up-regulating intercellular adhesion, down-regulating ACE2 level and immune-modulating effects. There are many evidences of Vitamin D against COVID-19 from the epidemiological, Clinical and meta-analysis findings. The further study will focused on the correlation between vitamin D supplementation and prevention and treatment of COVID-19 disease.

Keywords: covid-19, vitamin d, prevent, treatment.

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I. INTRODUCTION

Corona Virus Disease 2019 (COVID-19) is spreading worldwide. Now, there have been more than 8 millions cases and near 440 thousand deaths reported in over 200 countries . It is to be regretted that no effective drugs and vaccines have been used in clinical for prevention and therapy for COVOID -19 infection so far. During exploring new preventing and therapeutic measures , it is found that Vitamin D with VDR may reduce risk of COVID-19 by their impact on the intercellular tight adhesion of endothelial cells, down-regulating ACE2 level and stimulating innate and adaptive immune responses. Here, this paper reviews the mechanism and evidence of vitamin D against COVID-19.

II. THE MECHANISM OF VITAMIN D AGAINST COVID-19

2.1 Vitamin D up-regulating intercellular adhesion

Cell adhesion is the binding of a cell to a surface, extracellular matrix or another cell using cell adhesion proteins. Adhesion junctions (AJs) represent a multi-protein complex located at the lateral plasma membrane of contacting epithelial cells[1]. Intercellular adhesion is a mechanical barrier to prevent the invasion of various external pathogens (viruses, bacteria and fungi). The intercellular adhesion junction proteins mainly depends on E-cadherin, β-Catenin, claudins, Zonula occludens-1 (ZO-1), and Wnt/β-catenin signaling pathway. The combination of 1,25 (OH) 2D3 and VDR can protect the homeostasis of mucosal barrier by up regulating the expression of intercellular adhesion junction proteins and maintaining its integrity.

Vitamin D /VDR signaling and VDR-associated intracellular junction proteins(such as β-catenin and claudins) play key roles of tissue barriers in the pathogenesis of human diseases[1].

2.2 Vitamin D down-regulating ACE2 level

Angiotensin-converting enzyme 2 (ACE2) is the main host cell receptor of spike (S) proteins of COVID-19. ACE2 is expressed in type II alveolar cells of the lungs, absorptive enterocytes from the ileum and colon, esophagus upper and stratified epithelial, kidney proximal tubule cells, myocardial cells, bladder urothelial cells, and epithelial cells of the oral mucosa[2,3] (Zou et al. 2020; Xu et al. 2020). The high expression of ACE2 could be a potential risk factor for infection routes of COVID-19. As a result of COVID-19 infection, many patients develop acute respiratory

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distress syndrome (ARDS) and also lead to multiple organ damages. The data from several labs have demonstrated Vitamin D 1,25(OH)2D has the activities of decreasing ACE2 production and down-regulating ACE2 level , which affect coronavirus infections[4].

2.3 Vitamin D immune-modulating effects

The best-known function of vitamin D is to keep bones healthy. Besides, it also plays a role in other aspects of human healthy, especially regulates immune functions and antimicrobial activity. Vitamin deficiency has been reported in several diseases associated with increased inflammation and deregulation of the immune system. Vitamin receptor (VDR) is expressed by the majority immune cells, and vitamin D is able to convert 25(OH)D3 into its active form 1,25(OH)2D3 by immune cells. Vitamin D, VDR and its active form together show suppressive activity for autoimmunity and anti-inflammatory effect. In addition, they regulate the innate and adaptive responses. As an immune-modulator hormone, vitamin D has been known to play an important role in the immune system, so it could have protective and therapeutic effects against COVOID-19 and COVOID-19 infection –induced multiple organ damage.

2.3.1 Vitamin D regulates the Innate Response

The hormonal form of vitamin D3, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), is an immune system modulator and induces expression of the TLR coreceptor CD14. 1,25(OH)2D3 signals through the vitamin D receptor, a ligand-stimulated transcription factor that recognizes specific DNA sequences called vitamin D response elements. 1,25(OH)2D3 is a direct regulator of antimicrobial innate immune responses. The promoters of the human cathelicidin antimicrobial peptide (CAMP) and defensing-2 (defB2) genes contain consensus vitamin D response elements that mediate 1,25(OH)2D3-dependent gene expression. 1,25(OH)2D3 induces antimicrobial peptide gene expression in isolated human keratinocytes, monocytes and neutrophils, and human cell lines, and 1,25(OH)2D3 along with LPS synergistically induce camp expression in neutrophils. Moreover, 1,25(OH)2D3 induces corresponding increases in antimicrobial proteins and secretion of antimicrobial activity against pathogens. 1,25(OH)2D3 thus directly regulates antimicrobial peptide gene expression, revealing the potential of its analogues in treatment of opportunistic infections[11].

2.3.1.1 Pathogen Recognition Receptors(PRRs)

The crucial points for the innate immune response are the Toll-like receptors (TLRs), being a subgroup of various intracellular innate PRRs, which is present in macrophages, polymorphonuclear cells, monocytes, and epithelial cells. TLRs recognize molecules related to the pathogen; for example, the lipopolysaccharides of viral nucleic acids and proteins. Such activated TLRs release cytokines which induce reactive oxygen species and antimicrobial peptides (AMPs), cathelicidins, and defensins [12-16]. Several TLRs affect or are affected by VDR induction. For example, expression of the coreceptor for TLR4, a costimulatory molecule CD-14, is induced by 1α,25(OH)2D in monocytes and epidermal keratinocytes. In turn, the increased expression of CYP27B1 in macrophages is the indirect result of AMPs, which stimulates TLR2 [13].

The inflammatory cytokines TNFα and interleukins (IL) IL-1β, -6, and -12 are produced at an early stage of the innate immune response. These cytokines, among others, induce synthesis of acute phase proteins and contribute to the recruitment and activation of cells of the adaptive immune response. PRR signalling also results in the production of chemokine ligands (CXCLs), such as CXCL8–CXCL10 and IL-15, which generates neutrophils and natural killer cells (NK)[14].

2.3.1.2 Antimicrobial Peptides—AMPs

Vitamin D is involved in the regulation of about 1000 human genes. The only human cathelicidin, LL 37, enhances microbial killing against a broad

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range of respiratory pathogens and has a defined vitamin D- dependent mechanism. Appropriate concentrations of vitamin D facilitate the ability of immune system to defend[17].

TLR-released AMPs have a broad spectrum of activity, not only microbial but also antiviral, and have been shown to inactivate the influenza virus [16]. The antiviral effects of AMPs are the result of, among other effects, the destruction of envelope proteins done by cathelicidins.

AMPs induce membrane disruption of pathogen. The majority of cathelicidin is stored in neutrophil granules, but also the other types of immune cells, as monocytes and NK and B lymphocytes can express hCAP18 [12]. Production of cathelicidins in human macrophages in vitro is stimulated by the active metabolite of vitamin D, 1α,25(OH)2D, via increased expression of the VDR [16].

Vitamin D also regulates the other type of AMPs: defensins. Human beta defensin 2 is modestly stimulated by 1α,25(OH)2D and its antiviral effects arise from chemoattractive properties for neutrophils and monocytes [12,16]. However, serum 25(OH)D concentration was not associated with levels of serum AMPs in patients with community-acquired pneumonia [16].

2.3.2 Vitamin D regulates the Adaptive Response

The expression of nuclear vitamin D receptors (VDR) and hydroxylase enzymes by immune cells has led to a surge of research into the potential role of vitamin D in maintaining immune homeostasis and preventing the development of autoimmune processes.

Antigen-presenting cells, essential for the initiation and maintenance of cell-mediated immune responses, can be inhibited directly by vitamin D. The expression of major histocompatibility complex (MHC) class II and co-stimulatory receptors is inhibited, as is the differentiation of monocytes to dendritic cells [18]. Inflammatory cytokine expression [e.g. interleukin (IL)-1a, IL-1b, tumor necrosis factor (TNF)-a] is also inhibited and the vitamin D-induced inhibition of IL-12 release by dendritic cells has a profound effect on T lymphocyte differentiation[19]. IL-12 stimulates the development of T helper type 1 (Th1) lymphocytes and inhibits the development of Th2 lymphocytes. Vitamin D is associated with a dosedependent reduction in transcription of Th1 cytokines such as IL-2, granulocyte–macrophage colony-stimulating factor (GM–CSF) and interferon (IFN)-g, and increased expression of the Th2 cytokines IL-4, -5 and -10 [20]. Conversely, vitamin D insufficiency deregulates the balance between types 1 and 2 responses, leading to overexpression of Th1 cytokines. Vitamin D also has potent antiproliferative effects on T cells, principally T helper cells, and suppresses B cell antibody production both directly and indirectly *in vitro* [21,22].

Inhibition of IL-12 expression by 1,25(OH)2D3 has been shown to be achieved by interfering with the nuclear factor kappa B (NF-kB) pathway, a key transcription factor for the induction of inflammatory cytokines. Activation and binding of NF-kB to the NF-kB binding site within the promoter of the p40 subunit of IL-12 are down-regulated by 1,25(OH)2D3 [19]. Paradoxically, however, 1,25(OH)2D3 can also activate NF-kB by stimulating inhibitor kappa B (IkB) phosphorylation/degradation [23]. A possible explanation for these contradictory findings is the recent observation that 1,25(OH)2D3 can exert a biphasic regulation of NF-kB, combining an early suppressive effect followed by a prolonged reactivation of NF-kB [24].

Perhaps one of the most important modulatory actions of 1,25(OH)2D3 is its effect on regulatory T cells (Tregs) which prevent the activation of peripheral autoreactive T cells. In the absence of 1,25(OH)2D3 the numbers and functions of Tregs are reduced, potentially contributing to the development of autoimmune diseases, such as multiple sclerosis and type 1 diabetes, where low vitamin D status is associated with an increased risk of developing these disorders [25,26]. The role of vitamin D in autoimmune diseases has been reviewed recently [29].

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In addition to immune cells, respiratory epithelial cells can also constitutively convert inactive 25(OH)D to 1,25(OH)2D3, enabling high local concentrations of active vitamin D to increase the expression of vitamin D-regulated genes with important innate immune functions [28].

2.3.2.1 T Lymphocytes

The basis of the adaptive response is: antigen presentation to B and T cells, and the antigen-stimulated production of antibodies and a wide spectrum of cytokines, chemokines, enzymes, and hormones. The initial observation related to the role of vitamin D in the immune system was the presence of the VDR in the activated lymphocytes [29]. Vitamin D acts as a modulator of T helper cell proliferation and cytokine production, but also through promoting Treg cells, which are responsible for anti-infectious action, for suppressing immune responses, and for limiting inflammatory processes [30].

2.3.2.2 B Lymphocytes

1α,25(OH)2D inhibits proliferation and acts as a proapoptotic agent in activated human B cells in vitro. Although it does not act on the production of these cells, it is thought to inhibit their differentiation [16]. As shown by Fang et al. [31] in mice, the immune protection induced by the influenza virus primary infection significantly relies on the presence of B lymphocytes. Some suppressive effects of 1α,25(OH)2D were noted with reference to immunoglobulin (Ig)-secreting B cells. 1α,25(OH)2D was specifically able to inhibit the development of them after mitogenic stimulation [32].

III. THE EVIDENCE OF VITAMIN D AGAINST COVID-19

3.1 Epidemiological findings

WHO declared SARS-CoV-2 a global pandemic. The mean levels of vitamin D for 20 European countries and morbidity and mortality caused by COVID-19 were acquired. Negative correlations between mean levels of vitamin D (average 56 mmol/L, STDEV 10.61) in each country and the number of COVID-19 cases/1 M (mean 295.95, STDEV 298.7, and mortality/1 M (mean 5.96, STDEV 15.13) were observed. Vitamin D levels are severely low in the aging population especially in Spain, Italy and Switzerland. This is also the most vulnerable group of the population in relation to COVID-19[33].

The European Calcified Tissue Society Working Group has defined severe vitamin D deficiency as a serum 25(OH)D level lower than 30 nmol/L [34]. The Seneca study showed a mean serum vitamin D level of 26 nmol/L in Spain, 28 nmol/L in Italy and 45 nmol/L in the Nordic countries, in older people [34]. In Switzerland, mean vitamin D level is 23 nmol/L in nursing homes and in Italy 76% of women over 70 years of age have been found to have irculating levels below 30 nmol/L[34]. These are the countries with high number of cases of COVID-19 and the aging people is the group with the highest risk for morbidity and mortality with SARS-CoV2. Isaia et al. reported 25(OH)D circulating levels less than 12 ng/mL (30 nmol/L) in 76% of Italian women over 70 years of age, in late Winter [35].

Vitamin D deficiency is a major public health problem worldwide in all age groups [36,37] but vitamin D status deteriorates with age, above 70 years of life, due to decreased sun exposure and cutaneous synthesis[38]. It is poor in the institutionalized people, 75% of them being severely vitamin D deficient (serum 25(OH) D < 25 nmol/L) [34].

3.2 The Clinical findings

Low vitamin D levels have been associated with an increase in inflammatory cytokines and a significantly increased risk of pneumonia and viral upper respiratory tract infections. Vitamin D deficiency is associated with an increase in thrombotic episodes, which are frequently observed in COVID-19. A higher mortality in COVID-19 has been found to occur in patients with vitamin D deficiency[39].

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COVID-19 infection is associated with the increased production of pro-inflammatory cytokines [40], C-reactive protein [9], increased risk of pneumonia [40], sepsis [41], acute respiratory distress syndrome [41], and heart failure [41]. case-fatality rates (CFRs) in China were 6%–10% for those with cardiovascular disease, chronic respiratory tract disease, diabetes, and hypertension [42].

Serum 25(OH)D concentrations are inverse correlation with severe cases associated with pneumonia [43,44], increased production of pro-inflammatory [45,46], Increased C-reactive protein [47,48], increased risk of sepsis [49,50], risk of acute respiratory distress syndrome [51,52], risk of heart failure [53,54] and risk of diabetes mellitus [55,56,57]. Some findings for vitamin D supplementation in reducing the clinical effects of COVID-19 infection found from treating other diseases. Vitamin D deficiency contributes to development of Acute respiratory distress syndrome [52,58]. Baseline 25(OH)D 20 ng/ml achieved 40 ng/mL can have treatment of community-acquired pneumonia with vitamin D[59]. Vitamin D supplementation can reduce concentration of IL-6(pro-inflammatory cytokine) [60], can reduce C-reactive protein in diabetic patients [61]

There is a 12% overall protective effect of vitamin D supplementation against bacterial and viral acute respiratory tract infection (adjusted OD =0.88, p < 0.001) in 11,321 patients[62]. These protective effects increased to 19% in those individuals on the daily or weekly regimen of vitamin D compared to those dosing on a monthly bolus of vitamin D (adjusted OD = 0.81, p < 0.001). Furthermore, there is a 70% protective effect when vitamin D deficiency is corrected with supplementation (adjusted OD = 0.30, p = 0.006) [62]. This result is pertinent to the majority of individuals residing in the northern latitudes that experience vitamin D deficiency (serum 25(OH)D <25 nmol/L) due to extended periods of lack of sunlight.

To control for possible confounding of age, sex, and comorbidity on the association of Vitamin D status and mortality outcome, a generalized linear model was employed in the retrospective human study with 780 cases with confirmed infection of SARS-CoV-2 in Indonesia. After accounting for these variables in the model, a significant association has been obtained between Vitamin D status and mortality. In particular, the odds of death was higher in cases with insufficient Vitamin D status (OR=7.63; p<0.001). When compared to cases with normal Vitamin D status, death was approximately 10.12 times more likely for Vitamin D deficient cases (OR=10.12; p<0.001) [63].

3.3 The meta-analysis

Vitamin D is known to mitigate the scope of acquired immunity and regenerate endothelial lining. This may be beneficial in minimizing the alveolar damage caused in ARDS. Level I evidence (N = 11,321) showed that there is a 12% overall protective effect of vitamin D supplementation against bacterial and viral acute respiratory tract infections (adjusted OD =0.88, p < 0.001) [64]. These protective effects increased to 19% in those individuals on the daily or weekly regimen of vitamin D compared to those dosing on a monthly bolus of vitamin D (adjusted OD = 0.81, p < 0.001). Furthermore, there is a 70% protective effect when vitamin D deficiency is corrected with supplementation (adjusted OD = 0.30, p = 0.006) [64]. This result is pertinent to the majority of individuals residing in the northern latitudes that experience vitamin D deficiency (serum 25-hydroxyVitamin D <25 nmol/L) due to extended periods of lack of sunlight.

Association between 25(OH)D Concentration and Risk of Acute Respiratory Tract Infection (ARTI). We included 14 of the 16 studies that assessed the association between 25(OH)D concentration and risk of ARTI in the meta-analysis comparing the risk of ARTI in the lowest versus the highest 25(OH)D category (N participants = 78,127) and 10 studies were included in the trend analysis (N participants = 69,048). Five studies reported risk of ARTI in at least three categories of 25(OH)D concentration and the number of cases by

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exposure category; these were included in the evaluation of whether there is a non-linear relationship between ARTI risk and 25(OH)D concentration (N participants = 37,902). There was a significantly higher risk of ARTI in the lowest compared with the highest 25(OH)D category (pooled OR 1.83; 95% CI 1.42–2.37; I2 = 78.8%; p < 0.001). The pooled OR per 10 nmol/L decrease in 25(OH)D was 1.02 (95% CI 0.97–1.07; I2 = 72.7%; p < 0.001). There was a significant non-linear relationship (p for non-linearity = 0.029) with inflexion points at 60 nmol/L and 37.5 nmol/L. The steepest increased risk occurred below 37.5 nmol/L. Although both linear and spline models were significant, the spline model fitted the data better [65].

Association between 25(OH)D Concentration and Severity of ARTI. Five studies (N participants = 1495) were included in the meta-analysis of the odds of severe ARTI or mortality combined, comparing the highest and the lowest 25(OH)D category and four studies (N participants = 1422) were included in the mortality meta-analysis. The pooled ORs for severity/mortality combined and mortality separately were 2.46 (95% CI 1.65–3.66; I2 = 49.8%; p = 0.093) and 3.00 (95% CI 1.89–4.78; I2 = 66.7%; p = 0.029), respectively. The duration of ARTI was also inversely associated with 25(OH)D concentration; low 25(OH)D concentration was associated with a more prolonged ARTI in 7 out of 10 studies [65].

IV. CONCLUSION

Currently basic and clinical research results have shown some benefits of vitamin D for COVOID-19 infection, but these are only primary results. To assess whether there may be a correlation between vitamin D status and severity of COVID-19 disease as well as there may be a protective effect of vitamin D supplementation against severe COVID-19 is needed. We are waiting for the results of ongoing clinical trials that are registered to explore the relationship between vitamin D and COVID-19 [66,67].

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GLA-100 Versus GLA -300 as Add on Basal Insulin in Basal Supported Oral Therapy – Real World Evidence from Eastern India

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ABSTRACT

Introduction: Glargine U300 (GLA-300) has a better pK/pD profile compared to Glargine U100 (GLA-100) resulting in a flatter action profile that fulfills the criterion of an ideal basal insulin . This retrospective real world study from Eastern India looks at the efficacy and safety of GLA-300 compared to GLA-100 used in insulin naive diabetic subjects presenting with oral anti diabetic (OAD) failure.

Materials and Methods: Anthropometric data, blood pressure, glycaemic parameters, creatinine, and insulin dosage at baseline and after a treatment period of 12 weeks were taken up for analysis retrospectively.

Results: Fasting, postprandial and HbA1C values were reduced significantly for both 54 patients in GLA-300 arm and 50 patients in GLA-100 arm. No change observed in anthropometric parameters, blood pressure and creatinine values between the two arms. Incremental dose of +5.41±0.69 units for GLA-300 cohort was required in contrast to 10.66±1.04 units for GLA 100 cohort. There were 6 episodes of hypoglycaemia in the GLA-300 cohort and 11 in the GLA-100 cohort.

Conclusion: GLA-300 appears to be a safer compared to GLA 100 as effective basal insulin.

Keywords: insulin glargine, treatment outcome, hypoglycemia, basal supported oral therapy.

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I. INTRODUCTION

Type 2 Diabetes Mellitus (T2D) is a disorder whose pathophysiology has evolved from the lack of insulin to the concept of ominous octet (1). Whether it be beta cell apoptosis (2) or dedifferentiation of beta cells to alfa cells (3) - the fact remains that the beta cell function in T2D subjects decline with time (4). During progression in the continuum of the disease there is oral antidiabetic drug (OAD) failure (5) – meaning only oral agents against diabetes at that point of time are unable to maintain the glycaemic targets.

Recently the concept of basal supported oral therapy (BOT) has gained strong grounds (6) wherein along with other permissible OADs, a basal insulin is initiated and titrated to achieve glycaemic target and to maintain it. The simple regimens available for basal insulin initiation and titration have paved the path for early insulin initiation.BOT, since its inception, used GLA-100 (Glargine U100) as the basal insulin, accepting the fact that the U100 version of Glargine was not an ideal basal insulin because of a small peak in between 6-8 hrs of its time action profile. (7). In early 2018, GLA-300 (Glargine U 300) was introduced in India with a better demonstrated PK /PD profile leading to ideal 24-hour coverage and a peakless time action profile (8) - thereby putting the "gold standard basal insulin "label attached to GLA-100 under the scanner. With availability of GLA-300, it's use as basal insulin in

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BOT patients began to increase. Here, we retrospectively looked at the electronic medical records (EMR) to tease out data of patients on BOT receiving GLA-100 or GLA-300 for at least 12 weeks, to compare their efficacy and safety .

II. MATERIALS AND METHODS

This is a retrospective real-world registry based observational study carried out at the Endocrinology outpatient department of a tertiary care hospital of India between 1st June 2018 and March 31st, 2019. Insulin naive subjects on OAD who presented with osmotic symptoms and /or conformed to the Insulin initiation criteria of the Indian Insulin Initiation Guidelines (11) and were initiated on GLA-100 or GLA-300 (according to patients' choice due to price variability) at the Endocrine department were taken up for analysis.

2.1 Inclusion criteria

1. Insulin naive subjects on OAD who were on GLA100 or GLA 300
2. Patients who were followed up for at least 12 weeks
3. Patients who followed the titration algorithm provided by the Department as per glucometry values and maintained the complete dataset.
4. Patients whose age was between 18-70 years.

2.2 Exclusion criteria

1. Patients who required rescue prandial insulin
2. Patients with ill maintained dataset
3. Patients who dropped out of insulin therapy before completion of 12 weeks
4. Age below 18 years or greater than 70 years
5. Pregnant, intending to be pregnant or lactating mothers
6. Patients who were hospitalised during this 12-week study period

All patients who were initiated on Insulin were counselled to check fasting plasma glucose (FPG) weekly and empowered to titrate the insulin dosage according to a prespecified titration algorithm with telephonic assistance from departmental staff. The patients were recalled on week 2, week 4, week 8 and week 12 for dose titration as per the standard operating procedure (SOP) of the department. Patients receiving GLA 300 were started on an initial dose of 0.3 units/kg body weight as per the latest AACE guidelines (9) whereas GLA 100 was started at an initial dose of 10-14 units according to body weight as per existing SOP of the Department. Anthropometric data, blood pressure, glycaemic parameters, creatinine, and insulin dosage at baseline and after a treatment period of 12 weeks were taken up for analysis.

III. STATISTICAL METHODS

Descriptive and inferential statistics had been carried out in the present study. The measurements on the continuous scale were expressed as mean ± SD whereas the qualitative parameters were expressed as number and percentages. The baseline characteristics between the two arms were compared either by chi-square test or unpaired t-test. The changes in the study parameters from baseline to follow-up were assessed by paired t-test. Significance was assessed at a level of 5%. All data extracted were analysed using the Statistical Package for Social Sciences (SPSS) software version 21.0 (IBM Corp., North Castle, NY, USA).

IV. RESULTS

A total of 50 patients using GLA100 and 54 patients using GLA 300 were available after accounting for the inclusion and exclusion criteria. and their baseline characteristics are described in table 1.

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Table 1: Baseline Characteristics

	I-Glar U-100 Cohort, N=50	I-Glar U-300, N=54	p - value
Male, n (%)	23 (46)	29 (53.70)	0.432*
Female, n (%)	27 (54)	25 (46.30)	
Age(years), Mean ± SEM	56.56 ± 1.57	57 ± 1.01	0.972
Body weight (Kg), Mean ± SEM	69.65 ± 2.13	68.74 ± 1.85	0.894
SBP (mmHg), Mean ± SEM	132.22 ± 2.21	128.61 ± 1.64	0.261
DBP (mmHg), Mean ± SEM	80.56 ± 1.31	80.5± 1.26	0.943
BMI (kg/m2), Mean ± SEM	26.18 ± 0.73	29.14 ± 2.71	<0.001
FPG (mg/dL), Mean ± SEM	230.69 ± 7.49	206 ± 13.1	0.194
PPG (mg/dL), Mean ± SEM	295.18 ± 11.75	278.7 ± 19.19	0.452
HbA1c (%), Mean ± SEM	9.61 ± 0.22	9.12 ± 0.26	0.165
Insulin Dose (IU), Mean ± SEM	13.44 ± 0.41	22.85 ± 2.29	0.001
Serum Creatinine (mg/dL), Mean ± SEM	0.95 ± 0.03	0.90 ± 0.04	0.876

Age ,body weight, blood pressure and glycaemic parameters were similar between the GLA 100 and GLA 300 subgroups at the baseline

Table 2: Change in study parameters at the end of follow-up period

	I-Glar U-100 Cohort, N=50			I-Glar U-100 Cohort, N=54		
	Baseline, Mean ± SEM	Follow-up Mean ± SEM	p Value	Baseline, Mean ± SEM	Follow-up Mean ± SEM	p Value
Body weight (kg)	69.65 ± 2.13	69.58 ± 2.13	0.71	68.74 ± 1.85	69.5 ± 1.91	0.649
BMI (kg/m^2)	26.18 ± 0.73	25.97 ± 0.69	0.63	29.14 ± 2.71	29.39 ± 2.72	0.758
SBP (mmHg)	132.22 ± 2.21	127.6 ± 1.59	0.046	128.61 ± 1.64	126.9 ± 1.55	0.287
DBP (mmHg)	80.56 ± 1.31	80.26 ± 1.27	0.921	80.5± 1.26	79 ± 0.80	0.327
FPG (mg/dL)	230.69 ± 7.49	154.78 ± 7.59	<0.001	206 ± 13.1	152 ± 9.44	<0.001
PPG(mg/dL)	295.18 ± 11.75	236.37 ± 10.58	<0.001	278.7 ± 19.19	224 ± 14.8	<0.001
HbA_{1c} (%)	9.61 ± 0.22	8.56 ± 0.18	<0.001	9.12 ± 0.26	8.34 ± 0.22	<0.001
Serum Creatinine, (mg/dL)	0.95 ± 0.03	0.99 ± 0.03	0.901	0.90 ± 0.04	0.89 ± 0.04	0.632
Insulin Dose (IU)	13.44 ± 0.41	24.1 ± 1.45	<0.001	20.2 ± 1.72	25.61 ± 2.41	0.582

Table 3

	GLA 100	GLA 300	p - Value
Percent Change in Body weight, Mean ± SEM	- 0.09 ± 0.02	1.10 ± 0.84	0.207
Percent Change in BMI, Mean ± SEM	- 0.72 ± 0.20	0.85 ± 0.54	0.361
Percent Change in SBP, Mean ± SEM	- 3.49 ± 2.98	- 1.32 ± 3.69	0.857
Percent Change in DBP, Mean ± SEM	- 0.37 ± 1.21	- 1.79 ± 0.91	0.133
Percent Change in FPG, Mean ± SEM	- 32.90 ± 12.23	- 26.72 ± 8.44	0.042
Percent Change in PPG, Mean ± SEM	- 19.29 ± 3.89	- 19.71 ± 3.93	0.802
Percent Change in HbA_{1C}, Mean ± SEM	- 10.76 ± 2.22	- 8.55 ± 2.11	0.069

p< 0.05 considered as statistically significant, p computed by unpaired t-test

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There was statistically significant improvement of all glycaemic parameters (FPG, PPPG, HbA1C) in both the GLA 100 and GLA 300 cohorts. GLA 100 cohort showed substantial increase in the basal insulin dose between baseline and at 12-week. Percentage change in FPG was more in GLA 100 cohort than in GLA 300 arm and this change attained statistical significance (table 3)

Hypoglycaemia data was retrieved from the SMBG records and the updated EMR of the department. There were 6 episodes of hypoglycaemia in the GLA 300 cohort whereas the GLA 100 arm reported 11 episodes. This numbers though appeared numerically different, did not achieve statistical significance (p= 0.215). Severe and nocturnal hypoglycemia was greater in the GLA100 arm than in the GLA 300 arm. Details of hypoglycaemia episodes recorded are enumerated in table 4.

Table 4: Hypoglycemia Profile

	GLA - 300	GLA - 100	p - Value
Overall hypoglycemia, no. of event	6	11	0.215
Severe hypoglycemia, no. of event	1	4	
Nocturnal hypoglycemia, no. of event	0	2	
Event rate, per patient year	0.48	0.95	

V. DISCUSSION

When we compared the GLA300 and GLA100 arm for glycaemic efficacy we saw that GLA100 reduced FPG by 75.90+/-0.90 mg/ dl whereas GLA 300 reduced FPG by 54+/-3.66 mg/dl and both reductions were statistically significant (p< 0.001).However when we looked at the percentage reduction of FPG in both arm (table 3) there existed a difference, where GLA 100 arm experienced a reduction of FPG greater than that in the GLA 300 arm which was statistically significant. (p=0.042).This greater reduction of FPG by GLA 100 can be attributed to its pK / pD profile whereby it had a peak in the morning time (being administered during late evening hours and having a peak in between 6-8 hours) whereas GLA 300 having a flat time action curve lacked the peak and lagged behind in FPG reduction.

When we looked at PPPG, it was reduced by 58.81+/-1.17 mg /dl in the GLA 100 arm and by 54.7+/-4.39 mg/dl in the GLA 300 arm, both reductions were statistically significant (p<0.001). HbA1C reduction in the GLA100 arm was 1.05+/-0.04% whereas in the GLA 300 arm it was 0.78+/-0.04% and both changes were individually statistically significant (p<0.001). However when we looked at the percentage reductions in PPPG and HbA1C in the two arms and compared the two variables there was no statistically significant difference between the two arms (p=0.802 for PPPG and p=0.069 for HbA1C). There was a considerable numerical difference in the HbA1C reduction between the two arms which is a possible resultant of the greater FPG reduction in the GLA 100 arm.

GLA 100 arm underwent a statistically significant up titration (p<0.001), whereas there was insignificant up titration in the GLA 300 arm. The initial dose of GLA 100 was between 10-14 units as per existing SOP of the Department and hence required more up titration. On the other hand, GLA 300 being a new molecule, the initiation dose was 20-24 units as per the recent guidelines of AACE and thus required minimal up titration. Creatinine, body weight, BMI, systolic and diastolic pressure values in both the arms did not record statistically significant change either over 12 week follow up or when compared as

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percentage reduction in these study variables. (table 2)

EDITION 3, an RCT which looked at insulin naive OAD failure subjects, (10) seemed to most appropriately match the cohort of patients included in this real world study (RWS). The mean age of patients in this RWS in the GLA100 arm was 56.56+/-1.57 years whereas in EDITION 3 it was 57.2 +/-10.3 years, the greater variability perhaps attributable to the much larger numbers (n=439) in EDITION 3. GLA 300 arm in our RWS had a mean age of 57+/-1.01 years whereas in EDITION 3 it was 58.2+/- 9.9 year. GLA 300 arm in the RWS had 53.70% males whereas in the RCT the percentage was 57.6, which are more or less comparable. However, in the GLA 100 arm, there was 46% males which was significantly lesser than the 57.2 % males reported in the GLA 100 arm in the RCT. A comparative table elucidating the differences in glycaemic parameters of the two arms in the RCT viz EDITION 3 versus our RWS is given in table5.

Table 5

	GLA – 100 RWS	GLA – 100 RCT	GLA – 300 RWS	GLA – 300 RCT
FPG Reduction	-75.90+/-0.90 mg/dl	68.4+/-1.98mg/dl	54.+/- 3.66mg/dl	61.38+/-1.8 mg/dl
HbA_{1C} Reduction	-1.05+/-0.04 %	-1.46+/- 0.05 %	0.78+/-0.04%	-1.42+/-0.05%

The GLA 300 arm achieved a HbA1C reduction of -1.42 +/- (0.05)% at the 6-month mark in EDITION 3 whereas the reduction was -0.78 +/- (0.04) % at the 12 week mark in our RWS, a much lower figure which may be attributed to the difference in time period of the two studies. It may however be noted that the reduction of FPG was more with GLA 100 than with GLA 300 in both the RCT and our RWS.

There were 6 episodes of documented hypoglycaemia in the GLA-300 arm whereas there were 11 episodes of documented hypoglycaemia in the GLA-100 arm. (table 4) In the GLA 100 arm there were 4 episodes of severe hypoglycaemia requiring third party assistance, of which 2 were nocturnal. When anualised calculation was done, 0.95 events of hypoglycaemia/patient/year in the GLA-100 arm and 0.48 events of hypoglycaemia/patient/year in the GLA-300 arm was recorded in our RWS. The annualised event rate of hypoglycaemia was 6.8 events/patient/year in the GLA 300 arm and 8.5 events/patient/year for GLA 100 in EDITION 3. Hypoglycemia events are reported to be low during the initial titration phase of GLA-300 compared to GLA-100.[11] Even if we consider the annualized event rate of first 8 weeks titration phase data for GLA 300, the event rates were 4.5 events/patient/year in the RCT which is still higher than our RWS.

This significant difference in event rates of hypoglycaemia in both the GLA-100 and GLA-300 arm may be attributed to the shorter duration of our study period (only 12 weeks). Another contributing factor may be less aggressive monitoring in the RWS (weekly once and when symptomatic) in comparison to the conventional intensive monitoring in RCT (EDITION 3). Finally, failure to elucidate the non-documented mildly symptomatic and asymptomatic hypoglycaemia in both the arms may have also been an important contributor towards the low rates of hypoglycaemia obtained in our RWS.

Small sample size, short duration of study, minimal monitoing and failure to pickup the non documented asymptomatic hypoglycaemic episodes are the major limitations of our study. Studies with larger sample size with more frequent glucose monitoring are required to further validate the findings of this RWS.

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VI. CONCLUSION

As basal insulin therapy in insulin naive OAD failure patients, GLA 300 is equally efficacious as GLA 100 in reduction of glycemic parameters. With regards to hypoglycaemia GLA300 has the superior safety profile. These real-world findings are in line with the evidence shown in the EDITION 3 RCT.

Conflict Of Interest :

NONE

Funding :

NONE

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Comparison of the Sssperm Testing Kit with the Halosperm Testing Kit in the Analyzing Sperm DNA Fragmentation

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ABSTRACT

Objectives: Accuracy evaluation of testing kit analyzing sperm ADN fragmentation in infertile men, Comparison improved testing kit (SSSperm testing kit) and Halosperm testing kit in the analyzing sperm ADN fragmentation.

Subjects and methods: A cross-section study was conducted on 300 semen samples from infertile men with sperm concentration ≥1 million/ml, Use Bland-altman, T-Test, Pearson tip to compare.

Results: The SSSperm testing kit has Coefficient of variation CV% = 2,26% < 5%; t_{tn}=0,97 < t_c, 2 methods have similar results DFI (r = 0,995; p<0,001). The difference between the results of two methods is very small and not statistically significant (p = 0,236 > 0,05).

Conclusion: The SSSperm testing kit analyzing sperm ADN fragmentation is qualified of quantitative tests, and the SSSperm testing kit analyzing sperm ADN fragmentation is equivalent to Halosperm testing kit.

Keywords: sperm adn fragmentation, dfi, infertile, improved, comparison.

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Comparison of the Sssperm Testing Kit with the Halosperm Testing Kit in the Analyzing Sperm DNA Fragmentation

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SUMMARY

Objectives: Accuracy evaluation of testing kit analyzing sperm ADN fragmentation in infertile men, Comparison improved testing kit (SSSperm testing kit) and Halosperm testing kit in the analyzing sperm ADN fragmentation.

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I. INTRODUCTION

Infertility is defined as the inability to achieve a clinical pregnancy after at least 12 months of regular unprotected intercourse (1). Recently, infertility tends to increase quickly and becomes a global health problem(2).Globally, there are estimated 15% of married couples affected by infertility, and male infertility accounts for 30-40% of these cases(3) (4). Male infertility can be caused by a lot of causes as testicle injuries,sperm problem, hormon problem...(5) , and one of the most important causes is sperm DNA fragmentation which affect sperm function completion and male reproductive health(6).

Today,in the world, there are a lot of methods of testing sperm DNA fragmentation such as Comet, Tunel, SCSA, SCD ... but these methods require modern equipment, complex techniques and high prices(7)(8).

In 2003, Fernandez and partners proposed Sperm Chromatin Dispersion test to determine sperm DNA fragmentation. This method is based on the principle that the sperms without DNA fragmentation will form large halos around its nucleus, while the sperms with DNA fragmentation will not produce halos or produce very small halos around its nucleus when it is denatured in acidic environment and remove the nuclear protein (9). Based on this principle, Fernandez and partners created the Halosperm testing kit in 2005, since then, the researches of sperm DNA fragmentation using the SCD method or Halosperm testing kit have been published, contributed significantly to the diagnosis and treatment of male infertility.

In Vietnam, some hospitals and research institutes have used the Halosperm kit to diagnose sperm DNA fragmentation, but due to complete importation, the cost of test is still high and not suitable for most patients'condition. So that, our research team has built and evaluated

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the accuracy of an SSSperm testing kit to determine the degree of sperm DNA fragmentation by SCD method with the goal of completing the process and cutting the costs but still ensuring the quality of kit in assessment the degree of sperm DNA fragmentation of Vietnamese men. . However, at present, in Vietnam, there is no self-phase kit that can ensure the completeness as well as the accuracy of the test to determine the level of sperm DNA fragmentation. Therefore, we conducted this research with the aim of evaluating the equivalent of the SSSperm testing kit and the Halosperm testing kit using the Bland - Altman, T - test and Pearson test.

II. SUBJECTIVES AND RESEARCH METHOD

2.1 Subjectives

300 semen samples of male patients who were diagnosed with infertility at Hanoi Medical University Hospital, tested and assessed sperm DNA fragmentation at the Genetic counseling center, Hanoi Medical University hospital.

Selection criteria: Male patients aged from 18 years old, whose semen analysis has sperm density ≥ 1 million / ml and agree to participate in the research.

Exclusion criteria: Male patients who do not meet the above criteria, have genital cancer, are infected with HIV, syphilis, gonorrhea, have acute disease, mental illness and patients who disagree to participate in the research.

III. RESEARCH METHOD

3.1 Sample size

To complete the procedure, determine the accuracy, we use the formula to calculate sample size for a discriptive research according to S.K. Lwanga and Lemeshow's formula[5]:

$$n = Z^2_{1-\alpha/2}\frac{1-p}{\epsilon^2 p}$$

In which: 1- α/2 = 0.95; ε = 0.10; p = 95% (accuracy of reference procedure), n = number of required experiments, calculate at 21, we double and round to 50.

To compare SSSperm testing kit with Halosperm testing kit, we use formula to calculate sample size:

$$n = Z^2_{(1-\frac{\alpha}{2})}x\frac{p(1-p)}{(\varepsilon p)^2}$$

$Z_{(1-\alpha/2)}$: reliability coefficient (with 95% confidence ,Z= 1,96).

p: According to Duran E.H's research in 2002, the rate of high sperm DNA fragmentation >30% was p= 25% [7].

ε: we select 0,2.

n = $1{,}96^2$ x 0,25 x (1 – 0,25) : $(0{,}2 \times 0{,}25)^2$ = 147, rounded to 150.

We use a sample size of 300 to increase the accuracy.
So we used a sample size of 300.

3.2 Research design

A cross-sectional study.

3.3. Method of making templates

The test (using SSSperm testing kit) is improved based on Fernandez's SCD procedure (2003) [3], using Halosperm kit of Halotech as follows:

Step 1. Preparation of agar: Place agarose eppendorf tube into the float and melt using a water bath at 95 - 100 ° C for 5 minutes or in microwave for 3 minutes, until it is completely melted . Dilute semen samples with PBS solution so that the concentration of sperms is approximately <15 million / ml . Keep the agarose tube at 37 ° C for 5 minutes until the temperature of the eppendorf containing agar and the temperature of the incubator is balanced.

Step 2. Preparation of cell suspension : add 25 µl of semen to an agarose tube and mix well with a pipette. Keep the tube at 37 ° C and quickly take the next step, avoid agarose solidifying. Drip a drop of 25µl of cell suspension on a circular position on the microscope slide, cover the microscope slide, gently press, to prevent air bubbles from appearing. The microscope slide

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must be held horizontal throughout the entire process. Place the template in a refrigerator at 4 ° C, for 10 minutes, to allow agarose to solidify.

Step 3. After the cell suspension has solidified, remove the template from the refrigerator and remove the microscope slide by gently sliding away.

Preparation denatured solution and denaturation of sperm DNA: take 80 µl of denaturing solution into a tube containing 10ml of distilled water, shake well and we get the necessary denaturation solution. Place the template in the tray containing denaturing solution for 7 minutes.

Step 4. Cell lysis: take the template from denaturing solution and place in a tray containing 10 ml of lysis solution for 5 minutes.

Step 5. Wash the lysis solution: After finishing the lysis step, place the template in the tray containing distilled water for 5 minutes to wash the lysis solution.

Step 6. Dehydration: Dehydrate by adding the template to the alcohol solution for 6 minutes, then allow to air-dry.

Step 7. Dye the template: place the template horizontally, drip Giemsa solution 5 - 30% on the surface of the template, leave at room temperature for 10 minutes and then wash with water from the tap, avoid excessively washing which lightens the halo color.

IV. DATA PROCESSING

a) Evaluate the results

Observe the microscope slide under an optical microscope, and count at least 500 sperms on the template to determine the degree of sperm DNA fragmentation. Sperm DNA fragmentation was determined by sperm halo according to Fernandez et al.

The rate of DNA fragmentation (DFI - DNA Fragmentation Index) is determined by the following formula:

$$\frac{sperms\ \ having\ small\ halo+sperms\ \ having\ no\ halo+degenerative\ sperms}{Total\ counted\ sperms} \times 100\%$$

b) Data analysis

*To evaluate the accuracy of SSSperm testing kit

Evaluate accuracy of the testing kit through two indicators: trueness and precision [6]:

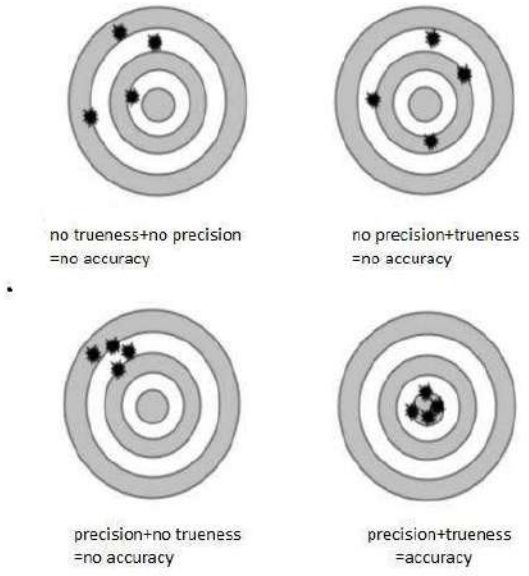

Figure 1: Illustration of accuracy [6]

Precision: Precision is the degree of variation of independent test results around the mean. Precision is a qualitative concept and is expressed quantitatively by standard deviation or coefficient of variation. The lower the precision is, the larger the standard deviation or coefficient of variation is.

$$SD = \sqrt{\frac{\sum\left(x_i - \bar{x}\right)^2}{n-1}}$$

$$RSD\% = CV\% = \frac{SD}{\bar{x}} \times 100$$

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In which:
SD: standard deviation
n : number of experiments
xi: Calculated value of the "i" experiment
$\overline{X}$: The average value of the experiments
RSD%: Relative standard deviation
CV%: Coefficient of variation

The precision can be classified into three following cases:

-Repeatability

Express the degree of accuracy or repeatability, the degree of variation among experiment results which are done in:
+ Same laboratory.
+ Same homogeneous sample.
+ The same inspector.
+ Same period of time.

Repeatability is determined by the method: on a patient's semen sample, use a improved kit (SSSperm kit) to determine the degree of sperm DNA fragmentation , repeat 10 times. Calculate SD standard deviation and CV% coefficient of variation with CV requirement ≤ 5%.

- Intermediate precision:

Express the accuracy of the method according to variables of laboratory :
+ For several days.
+ With different inspectors.
+ With different tools.

- Reproducibility
Express the accuracy of many laboratories conducting studies on the same homogeneous sample. Similar to repeatability provided that:

+ Change laboratory
+ Change method.

Trueness: indicates the degree of proximity between the average of the experimental results and the real value or accepted value is truly μ.

Determining the accuracy by the method : on a patient 's semen sample being determined the degree of sperm DNA fragmentation by Halos-perm kit, conduct experiment by using SSSperm testing kit, repeat 10 times, calculate the average value and standard deviation, from which the standard t_{tn} is calculated using the following formula, and then compared with Halosperm kit

$$t_{tn} = \frac{|\mu - \overline{x}|}{\sqrt{\frac{S^2}{n}}}$$

In which: t_{tn} : experimental t value

$t_t(\alpha,k)$: t value taken from table with statistical significant 0.5%

μ : real value or accepted value (reference)

$\overline{x}$: mean of experimental method

S^2 : variance of experimental method

n : number of experimental times

*To compare SSSperm testing kit with Halosperm testing kit:
Investigating the difference between the two methods is based on: Pearson correlation analysis, T - test and Bland-Altman plot using Epidata and SPSS.20 software.

V. ETHICAL RESEARCH

All the patients' information is kept confidential and only analyzed for fertility counseling for the patients and for this study, not for any other purposes.

VI. RESULTS AND DISCUSSION

*Accuracy evaluation of testing kit analyzing sperm ADN fragmentation in infertile men:

On a semen sample that had been identified DFI by using Halosperm kit, we used an improved kit(SSSperm kit) to determine the degree of sperm DNA fragmentation, repeated10 times. The results are in the following table:

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Table 1: Results of test determining the accuracy of the SSSperm kit

Time of Experiment	DFI (%)
1st	15,4
2st	15,0
3st	14,4
4st	14,2
5st	15,2
6st	15,2
7st	15,2
8st	15,0
9st	14,6
10st	15,0
Proof (made of Halo kit)	14,8

6.1: Precision

Because of conducting in the laboratory, we calculate the precision through the repeatability. From the above result table we get:

Table 2: Results of precision evaluation

The mean of DFI (%)	14,92
SD	0,391
CV%	2,62%

In experiments, especially in quantitative tests, there are many errors that affect the test, lead to inaccuracy in the results. Therefore, to control these confounding factors, it is necessary to use the concept of precision. The precision describing the results only depends on the random errors and do not relate to the actual results of the sample. The lower the precision is, the larger the standard deviation or coefficient of variation is, otherwise, the greater the precision is, the smaller the coefficient of variation is [6]. In this study, our improved kit has repeatability with coefficient of variation CV% = 2.62% .So, the coefficient of variation has a value not exceeding 5% according to the Vietnam Standards [6], this indicate that repeatability of the procedure meets the requirements of the analysis. Thus, when there are effects of random error factors, for the same sample, the degree of sperm DNA fragmentation determined under different conditions has errors within the acceptable range.

Compared with the commercial Halosperm kit of Fernandez which has an actual coefficient of variation of 5.3% [7]; higher than the SSSperm kit. This proves that the SSSperm kit meets the standards of a testing kit.

6.2: Trueness

Trueness indicates the degree of proximity between the average values of the experiment results and the real values or accepted values are true

With experimental testing the trueness, we calculate t_{tn}= 0,97; Besides, through searching tables, t_c = 2,262 [6]. Thus $t_{tn} < t_c$. This means that the sperm DNA fragmentation index determined by the SSSperm kit has the same results as by the commercial Halosperm kit. The process achieves the accuracy as requirements of an analysis.

Thus, the precision and the trueness of the SSSperm kit completely meet the requirements of a testing kit according to Vietnamese Standards. This is the first step of the project.

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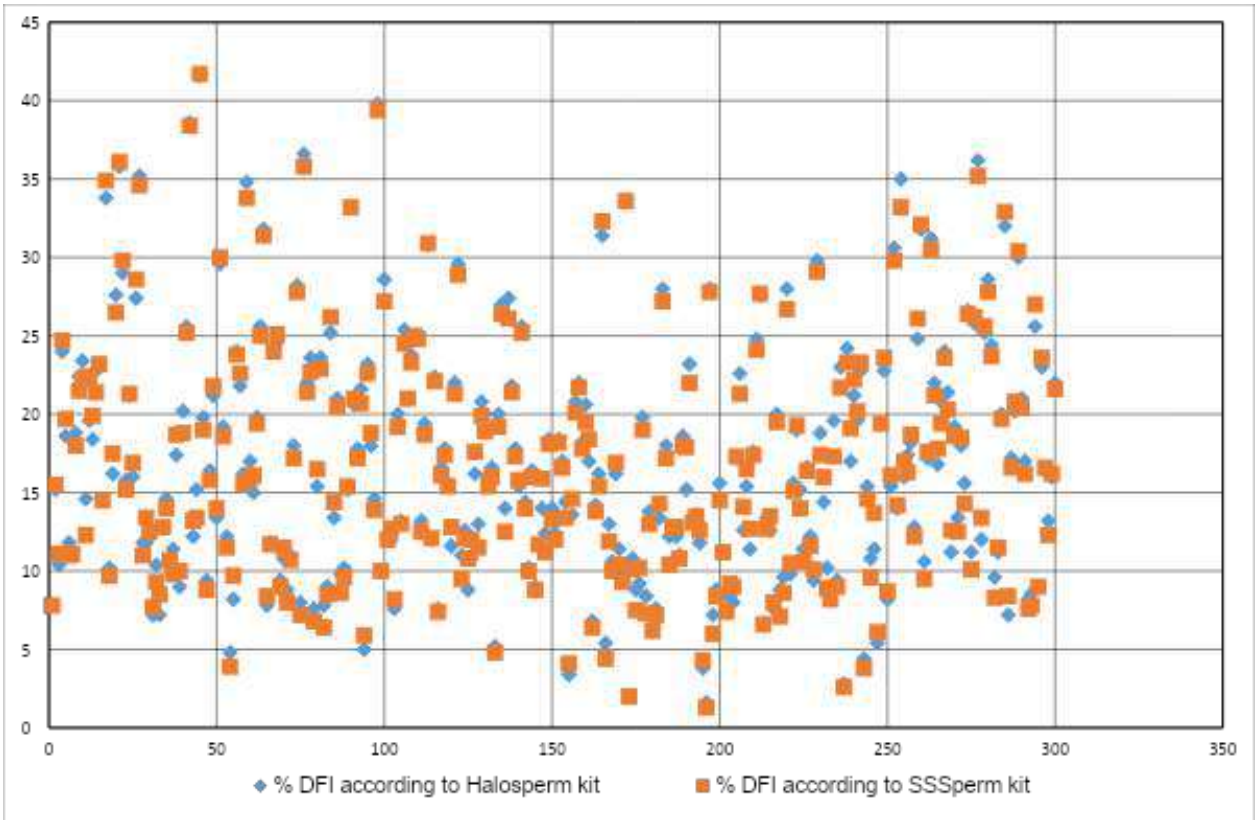
- *Compare SSSperm kit with halosperm kit*

We have developed an improved procedure for determining the level of sperm DNA fragmentation that is different from the Halosperm testi kit at the following key points:

Table 3: Improvements in techniques for testing sperm DNA fragmentation

	Fernandez et al, 2003 [6]	SSSperm testing kit
Denaturing solution	Denaturing solution of kit	HCl 0.29%
Lysis solution	Lysis solution 1: 0,4 M Tris-HCl; 0,8 M DTT; 50 mM EDTA; 1% SDS, pH 7,5. Lysis solution 2: 0,4 M Tris -HCl; 2 M NaCl; 1% SDS, pH 7,5	0,2 M Tris ; 0,1M DTT 2 M NaCl ; 1% Triton, pH 7,5
Dehydration	3 steps with alcohol 70%, 90% and 100%	1 step with alcohol 100%
Dyes	Wright	Giemsa

After completing the SSSperm testing kit, we took 300 semen samples to make templates to assess the degree of sperm DNA fragmentation by 2 methods with the Halosperm testing kit and SSSperm testing kit. Our results are shown in following chart:



Comment:

Value of the sperm DNA fragmentation index (DFI) measured by the Halosperm commercial kit and the SSSperm testing kit are almost similar.

To compare two kit more accurately, we Pearson test, T - test and build Bland - Altm plot.

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Table 4: Table of testing correlation coefficient between two methods

N		300
Pearson correlation coefficient		0,995
p		< 0,001
confidence interval 95 %	Upper limit	0,996
	Lower limit	0,994

Comment:

Pearson test showed a strong and significant correlation between sperm DNA fragmentation index measured by two methods : using SSSperm testing kit and commercial Halosperm kit with r = 0.995; p <0.001.

Table 5: T-test table

t	p	The mean of the difference	confidence interval 95%	
			Lower limit	Upper limit
1,187	0,236	-0,010	-0,003	0,011

Comment:

Results of assessing the level of sperm DNA fragmentation by using SSSperm kit and by using commercial Halosperm kit do not have statistically significant differences with 95% confidence level (p = 0.236> 0 , 05).

Using Bland - Altman plot which is used to quantify the compatibility between two different measurements or to compare a new test with a standard recognized test.

From the above tests, we have built a Bland Altman plot showing the compatibility between measurement results of two methods:

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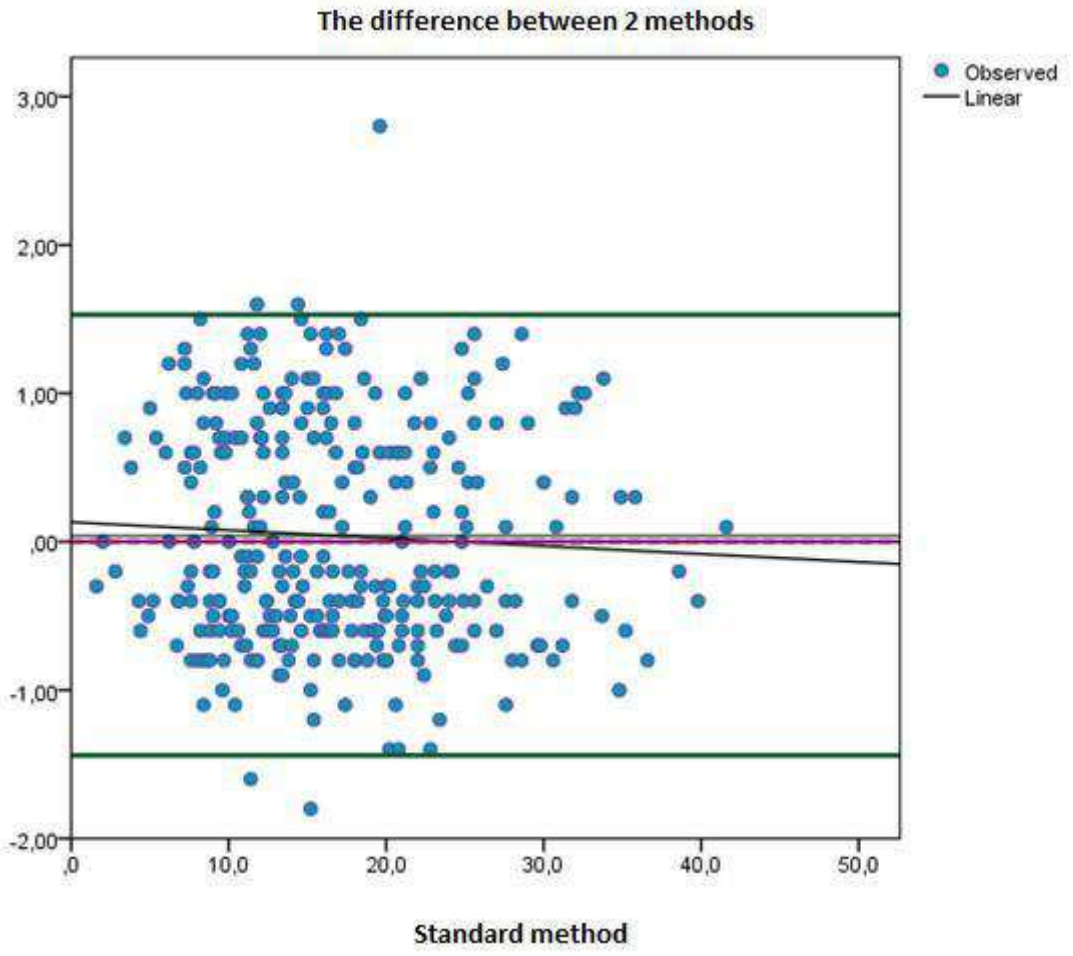

Figure 2: Bland Altman plot showing the compatibility of the two measurement methods

Comment:

The difference of mean between the two methods is very small (0.042). Most cases have errors within the limit of ± 1.96 standard deviations. Therefore, the two methods : testing by SSSperm kit and commercial Halosperm kit have the same value in determining the degree of sperm DNA fragmentation.

VII. DISCUSSION

Sperm with fragmented DNA inable to produce the halo of dispersed DNA loops while the normal sperms succeed in producing the halo after treatment with denaturing agent and removing nuclear protein.Basing on this principle, we created an improved test (SSSperm kit) to determine sperm DNA fragmentation.

What are the advantages of the SSSperm kit and the differences between the improved test and other existing tests ?

The improved test is a quantitive test . Unlike semiquantive tests as COMET, TUNEL....which determine sperm DNA fragmentation by determining color and flourscence intensity, the improved test determines sperm DNA fragmentation by measuring percentage of sperms with nondispersed (have no halo or small halos) or dispersed DNA loops (have large halos), which can be looked with naked eyes.

Halosperm testing kit which is also based on principle that the sperms with fragmented DNA fail to produce halos while normal sperms produce large halos was published by Fernandez et al in 2003 .There have been some researches conducted to evaluate the value of this kit(9) . The results obtained from these reseaches indicated

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that this testing kit meets the accuracy requirement to determine sperm DNA fragmentation and it has been used widely in diagnosing male infertility especially in Viet Nam .

However the price of this kit is still high which is not suitable for many of VietNamese . Therefore , we created the improved testing kit(SSSperm testing kit) which is simpler and cheaper than Halosperm testing kit but still ensures the quality of the new kit. When we use Pearson test, T-test and Bland –Altman plot to compare the SSSperm testing kit with Halosperm testing kit, the results indicated that there were sigfinicant correlations between the two kits ($r^{=}0.995, p<0.001$), the mean of difference was -0.01, $p^{=}0.236>0.05$, the difference was not statically significant.

In conclusion, the improved test is accurate, fast, inexpensive and simple . Therefore , the SSSperm testing kit should be used as a routine kit in Viet Nam to determine sperm DNA fragmentation for infertile men.

VIII. CONCLUSION

The SSSperm testing kit has the required accuracy of a quantitative testing kit (with CV% = 2.62% <5% and ttn = 0.97 <tc).

Result obtained from improved process is equivalent to the commercial Halosperm kit. Differences in the results obtained from the two methods are not statistically significant, and are completely random.

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Nurse Compliance using basic Personal Protective Equipment in Providing Health Services Nursing Actions

Suprapto

ABSTRACT

Background: Personal protective equipment is a tool used by a person in his work that is intended to protect himself from certain sources of danger both from work and the work environment and is useful in reducing or preventing disability. Objectives: This needs serious attention by examining nurses' compliance in using Personal Protective Equipment when providing nursing services to reduce the incidence of nosocomial infections and work disabilities.

Methods: This research was conducted by descriptive method, sample selection with total sampling. The number of samples studied was 40 respondents. Data was collected from patients using the nurse's compliance questionnaire in using hands on personal protective equipment and masks as well as observing nurses' compliance in using hands on personal protective equipment and masks as well as the availability of supplies of personal protective equipment in the emergency room.

Keywords: compliance, personal protective equipment, nurse.

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Methods: This research was conducted by descriptive method, sample selection with total sampling. The number of samples studied was 40 respondents. Data was collected from patients using the nurse's compliance questionnaire in using hands on personal protective equipment and masks as well as observing nurses' compliance in using hands on personal protective equipment and masks as well as the availability of supplies of personal protective equipment in the emergency room.

Results: Nurse compliance research in using personal protective equipment in the emergency room is maximum of 85% and there are still 15% non-adherents and the supply of equipment for personal protective equipment in the emergency room is still limited, especially for personal protective equipment masks.

Conclusion: Influenced by respondent's age, last education and length of work and availability of personal protective equipment. It is expected that the parties pay attention to their employees in their compliance with personal protective equipment while working and facilitate the availability of personal protective equipment in each room, especially in emergency rooms that serve a large number of patients in a day.

Keywords: compliance, personal protective equipment, nurse.

I. INTRODUCTION

Control methods can be done to reduce hazards in the work environment where the best way is to eliminate the hazard or close the source of the danger, if possible but often these dangers cannot be completely controlled and therefore efforts are needed to prevent them by using some personal protective equipment [(1)]. Personal protective equipment is a tool that is used by someone in their work which is intended to protect them selves from certain sources of danger both from work and the work environment and is useful in reducing or preventing disability, there are some nurses who do not obediently wear gloves and masks when going give action to the patient, the nurse wears gloves that do not match the size, and wears gloves that are not sterile. Nurses assume not all actions must wear gloves and masks. These results indicate that nurses' compliance in wearing personal protective equipment is not compliant[(2)].

The results showed statistical results at a significant level α <0.05 obtained there was a strong relationship between knowledge of nurses with compliance using personal protective equipment according to SOP (ρ value = 0.024), there was a significant relationship between

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nurses' attitudes with adherence using appropriate personal protective equipment SOP (ρ value = 0.027), and there is no meaningful difference between nurses' actions and compliance using personal protective equipment according to SOP (ρ value = 0.100), in the BLUD inpatient room of Konawe Regency Hospital in 2015[3]. Based on the simultaneous test is 84.1%, it is very strong that surgical nurse compliance is really real/significantly influenced by behavioral factors that are variables in this study, namely: attitude, length of work, supervision, availability of PPE, peers, perception and only 15, Only 9% of other factors outside the variables used in this study could affect nurses' compliance in using PPE in IBS Ulin Hospital Banjarmasin. Banjarmasin[4].

Obedience is like obeying orders, obeying orders or rules. Whereas obedience is behavior according to the rules and discipline. The work of operators in the Coal Yard is a job that requires expertise, creativity and a high concentration in doing work because the workplace is exposed to a lot of coal dust, besides the means of personal protective equipment (PPE) is an important component in reducing the exposure of coal dust to operator worker[5]. The factors that influence the enabling factors are the lack of means of supporting PPE, SOPs are not yet available about PPE, while the reinforcing factor is due to the lack of socialization about PPE, oversight that is still lacking, there are no sanctions or rewards for those who obey or are not compliant to use PPE. Health status is influenced by predisposing factors, enabling factors, reinforcing factors and compliance with PPE use by 45.7% while 54.3% is influenced by other variables[6].

Preparation of fixed procedures or operational standard procedures governing personal protective equipment in hospitals, will reduce the risk of a nurse being infected by the disease so that the safety of nurses' work will be more secure and the provision of nursing care will be of better quality because it is carried out according to existing operational standards. Each hospital certainly has a standard operational procedure of action that must be followed by every health worker, but there are still health workers who do not use basic personal protective equipment.

II. MATERIALS AND METHODS

The research design used is descriptive design. This study aims to identify nurses' compliance in using personal protective equipment in the emergency room at the Makassar General Hospital. In particular, it also wants to know how nurses' habits in using personal protective equipment in providing nursing care services. Research with a descriptive design aims to describe (describe) urgent events that occur in the current conditions. Descriptive activity is carried out systematically and emphasizes more on factual data than the conclusion.

The population in this study were all nurses in the emergency room with a total of 40 people. The sample is a portion of the whole object examined which is considered to represent the entire population. In this study the sample was all nurses who served in the emergency unit. Determination of the number of samples using total sampling techniques how to take this sample is to take all members of the population into the sample because of limited population.

Multivariate analysis was carried out to explain or describe the characteristics of the observed variables and measured based on the value of data distribution, namely the minimum and maximum values. The variables studied in the questionnaire were Nurse's compliance in using (handscon and mask) and also to know the age, sex and duration of work. personal protective equipment in the emergency room.

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III. RESULTS AND DISCUSSION

Table 1: Multivariate Tests

Obedient		Value	F	Hypothesis df	df	Sig.
Obedient	Pillai's Trace	.965	247.246[b]	4.000	36.000	.000
	Wilks' Lambda	.035	247.246[b]	4.000	36.000	.000
	Hotelling's Trace	27.472	247.246[b]	4.000	36.000	.000
	Roy's Largest Root	27.472	247.246[b]	4.000	36.000	.000

Based on the analysis shows that of the 40 respondents, the majority complied with the use of basic personal protective equipment handscoon and masks with a total of 34 (85%) and respondents who were not compliant in the use of basic personal protective equipment handscoon and masks when performing nursing actions amounted to 6 people (15%). The level of compliance of nurses in using personal protective equipment on duty in the emergency room can be categorized as compliant to the maximum (85%). But in this study there were still respondents who were not compliant in the use of personal protective equipment There were 6 (15%) respondents for various reasons.

Expressing compliance can be influenced by internal factors and external factors such as age, education, knowledge and years of service which suggests that the factors that affect compliance are education, age, and length of work[(7)]. That the majority of nurses in PKU Muhammadiyah Gombong Hospital have a good level of knowledge (88.3%). The majority of nurses at PKU Muhammadiyah Gombong Hospital have compliant behavior in the use of personal protective equipment (78.3%). There is a relationship between the level of knowledge of nurses with the level of compliance of nurses in the use of personal protective equipment for the prevention and reduction of risk of infection in PKU Muhammadiyah Gombong Hospital (p = 0,000)[(8)].

It can be concluded starting in terms of the age of the respondents 20-29 years (45%), 30-39 years (45%), and 40-49 years (10%) also affect one's compliance. That someone in old age is more adaptive so that in carrying out a procedure more quickly respond and do it correctly[(9)]. Inversely proportional to those stating that someone who is younger tends to have a strong physique and can work hard but in working less disciplined and less responsible[(10)].

The results of hypothesis testing using the Chi-square Test between the age variable and the nurse's compliance variable to the use of PPE showed a p-value of 0.779> 0.05, which means that Ha was refused Ho. So it can be concluded that there is no relationship between the age of the respondents with the level of compliance of respondents in using PPE[(11)].

Respondent education is also a factor that influences the compliance of nurses with DIII nursing education as many as 14 (35%), Nursing S1 as much as 20 (50%), and Nurse education 6 (15%), where education influences the individual mindset while the mindset influences one's behavior as well as will. Willingness is a basic impulse from within that is higher than instinct, reflexes, automatism, craving, habits, inclinations and passions. Willingness is the encouragement of the conscious mind based on consideration of thoughts and feelings and the whole person who causes activities directed at achieving certain goals related to the needs of his personal life[(12)]. This is perhaps what the nurses lacked. Although the level of knowledge is good because of the high level of education, but if there is no will they will

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not be obedient to use personal protective equipment[13]. In accordance with the statistical test results a significant value (ρ) = 0.296 where this value is greater than the value used which is α = 0.05. Conclusion: there is no significant relationship between the education level of emergency nurse nurses with compliance with the implementation of standard operating procedures for admission of new patients in AM Parikesit Tenggarong Hospital[14].

Length of work> 5 years (55%), 5-10 years (40%), and <10 years (5%) are also factors that influence compliance. According to Gibson (1997), the longer a person works the higher the level of achievement, the high achievement comes from good behavior in this case good behavior to use personal protective equipment while working.

Where someone who has worked for a long time is expected to better understand his work including the effects of his work. Supervision is the variable that contributes the most in influencing nurses in using personal protective equipment in the prevention of nosocomial infections in hospitals. Range It is recommended that the hospital be obliged to facilitate, complete the means of personal protective equipment in accordance with health and safety regulations and laws and is expected to the party hospitals, especially leaders or related officers must carry out inspection, inspection, control and various actions in supervision of the use of personal protective equipment. And it is expected to the hospital to give strict sanctions and awards to nurses to be motivated to wear personal protective equipment [15]. There is no relationship between the length of work of nurses with the attitude of compliance with SPO with the result p value = 0.943. The conclusion of the study there is no meaningful relationship between length of work with compliance, it is recommended that the hospital create a program that is able to make nurses adhere like supervision and performance evaluation which is more structured[16].

The longer a person works, the more skilled and more experienced in carrying out work. The performance meant performance in carrying out nursing care of course all nursing actions that have been prepared in accordance with nursing standards issued by the ministry of health and agencies in the form of standard operating procedures, as a manifestation of the professional attitude of nursing care of the Ministry of Health of the Republic of Indonesia has imposed the existence of standard operating procedures (SOP) [17]. Therefore compliance from the use of personal protective equipment is influenced by several factors, namely the age of the nurse, the last education and also the length of work that affects someone's compliance, it is expected that the implementing nurse so that in performing nursing actions do it according to the SOP which includes the use of protective equipment yourself at work and this may be an important study for hospital management in the emergency room so that in the future it can be known what exactly is the root of the problem there are still nurses who are not compliant in using personal protective equipment handscoon and masks so that solutions can be found to overcome them in the hope that these nurses can be motivated to always work according to standards including being motivated to always use hands on personal protective equipment and masks when perfor- ming nursing actions. to reduce the incidence of nosocomial infections and trans- mission of disease from patients to our bodies to keep ourselves safe at work.

IV. CONCLUSION

Based on research conducted at the Hospital of the emergency room unit, it can be concluded that: The level of compliance of nurses in using basic handcoon protective equipment and masks, is at a maximum level of 85%, only a small pro- portion of non- compliant 15% and the availability of basic personal protective equipment handscoon masks in the emergency room are quite limited, especially masks with a very limited amount in a day.

To reduce the incidence of nosocomial infections and disease transmission from patients to our body, and also to the responsible party of the

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hospital, especially for the emergency room to pay attention and give a warning if there are nursing nurses who bypass nursing procedures including in the use of personal protective equipment for the emergency room to be firm in overseeing the discipline of its employees so as to create a structured work environment and work according to standard operating procedures.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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