Title page

Diagnostic Value of IgA [EBNA1+VCA p-18] ELISA to Discriminate NPC Patients and Their Unaffected Family Members

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Abstract:

Several studies have revealed the importance of detecting antibodies against specific EBV antigens, particularly IgA, that can be predictive or prognostic for NPC. Otherwise, it is still needed more data about the distinction of EBV seroreactivity between the NPC and high risk unaffected individuals. The study is aimed to evaluating the sensitivity and specificity of IgA [EBNA1+VCA p-18] ELISA on histopathology diagnosis of nasopharyngeal carcinoma between NPC and high risk unaffected individuals (family members of NPC). A case controll study was conducted on 108 cases, consists of 47 NPC cases and 61 unaffected close family members as controls. Peripheral blood serum were tested for IgA [EBNA-1+VCA p-18] ELISA tests. Nasopharyngeal mucosal biopsies among NPC subjects were used as golden standard. The sensitivity and specificity, positive predictive value (PPV), and negative predictive value (NPV) of IgA-EBV ELISA were determined, by using cut off value (CoV) = 0.352. The sensitivity and specificity of IgA [EBNA1+ VCA p-18] ELISA were 95.7% and 77.1% respectively. The combination of sensitivity and specificity for serological diagnostic methods on NPC may be evaluated on ROC, which has area under curve (AUC) of 86.4%, or a good method for NPC diagnosis. The PPV and NPV of this test were 76.3% and 85.2%, respectively. The IgA-[EBNA1+VCA-p18] ELISA is a good method to discriminate NPC patients and their unaffected family members.

Keywords: sensitivity, specificity; IgA ELISA; NPC; unaffected family

1. Introduction

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Epstein - Barr virus (EBV) infection and environmental exposure are known to be the main cause of this malignancy(Chan, J.K.C., F. Bray, P. McCarron, W. Foo, A.W.M. Lee, 2005) (Chan, 2007). EBV reactivation of the nasopharynx mucosal epithelium is an important momentum in nasopharyngeal carcinogenesis, which can be detected by IgA antibodies against EBV VCA (Raab-Traub, 2002). Several studies have concluded that elevated IgA titers to EA, VCA and EBNA-1 are characteristic of nasopharyngeal malignancies, where the detection is very useful and superior as a combination of seromarker early diagnosis and prognosis (Cheng, JY., 2003)(Fachiroh, J., Paramita, DK., Hariwiyanto, B., Harijadi, A., 2006)(Karray, 2005)(Paramita, D.K., Fachiroh J., Haryana, S.M. and Middeldorp, 2009). However, a positive EBV antibody titer does not necessarily lead to KNF. Only less than 5% of individuals with IgA + became KNF (Chang, ET., and Adami, 2006), and the contribution of EBV / IgA / VCA antibody status to KNF risk was only 32.2% (Xiuchan-Guo, 2009).

The identification of IgA [EBNA1 + VCA p-18] in our preliminary study sample in Semarang obtained a positive (cut of value / CoV> 0.3524) titer on 10 of 22 (45.5%) healthy at risk individuals, and 34 of 40(85%) KNF sufferers. The study showed that high antibody titers of EBV in the city of Semarang. The previous study of Mubarika and friends in 2010 also reported that ELISA IgA antibody titers (EBNA1 + VCA-p18) in KNF patients and healthy and risky populations in Yogyakarta, Semarang, Malang and Makassar, obtained higher reactivity in samples from Semarang and Makassar than Yogyakarta. The results of this study are very interesting, because the examination of IgA from different regions shows different reactivity patterns. Therefore, further research is needed to capture KNF patients and healthy individuals from different regions, in order to know and compare the IgA reactivity patterns of each of these areas. The data obtained will be the reference for determining CoV and improving the reliability of the developed ELAA IgA [EBNA1 +

VCA-p18] system.

Viral risk detection is already present, ie by the identification of EBV antibody serum with a combination of EBNA1 and VCA-p18 marker IgA ELISA. This method has good sensitivity and specificity, making it the most sensitive, economical and simple early diagnostic method, especially for KNF screening in high-risk areas (Fachiroh, J., Paramita, DK., Hariwiyanto, B., Harijadi, A., 2006)(Paramita, D.K., Fachiroh J., Haryana, S.M. and Middeldorp, 2009).

2. Methods

2.1. Design and serum samples

Analytic observational studies with case control designs for KNF cases were matched to family relationships, or individuals with non-specific chronic disorders in the ENT area (rhinitis, epistaxis, nasal congestion, tinnitus, otitis and cephalgia). The place of research is conducted in Anatomical Pathology Laboratory of FK UNDIP and Laboratory of Molecular Biology of Faculty of Medicine UGM. The study time starts from March 2012 until the sample size is met. The control group is a healthy individual at risk (family history of KNF, risk of environmental exposure similar to that of KNF or a history of non-specific chronic disorders in the ENT area). The case group is KNF sufferers. The sample is part of an affordable population that meets the inclusion criteria for KNF patients (complete medical record data, KNF diagnosis according to WHO criteria 2005), for risky healthy individuals (not diagnosed with KNF and other malignancies, relates to KNF patients, or individuals living or Working in the environment around the patient, who have a non-specific chronic disorder in the ENT area).

2.2. IgA titers [EBNA1 + VCA p-18] ELISA

IgA titers [EBNA1 + VCA p-18] ELISA is a measurement of antibody response to EBV in blood serum examined by two step sandwich indirect ELISA according to method

(Fachiroh, J., Paramita, DK., Hariwiyanto, B., Harijadi, A., 2006). The examination was done at bio molecular Laboratory of UGM Faculty of Medicine, where the result of the reading with the ELISA reader OD 450 nm spectrophotometer in Duplo. The result of the measurement value is the mean of the two measurements. Determination of KNF risk limits using the value of cut ov value (CoV) obtained from the average titer of three normal individuals plus standard deviation (Fachiroh, 2012), which is equal to 0.352.

2.3. Ethical clearance

This study has obtained ethical approval from the Health Research Ethics Committee (KEPK) of the Faculty of Medicine, Diponegoro University and Dr. Kariadi Hospital Semarang.

3. Results

3.1. Characteristics of subjects on ELISA examination

The subjects examined IgA [EBNA1 + VCA p-18] ELISA were 108 of 189 samples, or there was a missing of 81 (42.9%). Chi-square Continuity correction test for gender variable of subjects conducted by IgA [EBNA-1 + VCA p-18] ELISA examination, with $\alpha = 0.05$, 95% confidence interval (CI) and 80% power get P value = 0.544, or no significant difference between case groups and controls. Pearson Chi-square test for age group variables showed a significant difference (P = 0.041) between case and control group (Table 1).

3.2. Titer IgA [EBNA-1+VCA p-18] ELISA Differences

Table 2a shows that 45 out of 47 cases have IgA [EBNA-1 + VCA p-18] ELISA titres larger than the cut of value (CoV $\geq$ 0.352), whereas in the control group 14 of 61 subjects. Chi-square Continuity correction test with $\alpha = 0.05$, 95% CI, and 80% power get P value = 0.00 or there is significant difference on urea IgA [EBNA-1 + VCA p-18] ELISA between case group and control. This result means that the titanium IgA [EBNA-1 + VCA p-18] ELISA is a measurement tool that can be used as a distinction between case and control groups.

Table 2b shows that the distribution of IgA [EBNA-1 + VCA p-18] titer frequency in men is higher than female, but Chi square continuous correction test with $\alpha = 0.05$, 95% CI, and power 80 % Get P value = 0.092, or there is no significant difference between men and women. This result means that the negative or positive probability for IgA [EBNA-1 + VCA p-18] ELITA titers between male and female is equal.

In table 2c, it is shown that the distribution of IgA [EBNA-1 + VCA p-18] titer frequency in older age (≥40 years) is greater than in younger age (<40 years). Chi-square Continuity correction test with $\alpha = 0.05$, 95% CI, and power 80% get P value = 0.002, or there is significant difference between old and young age. This result means that IgA [EBNA-1 + VCA p-18] ELISA titer tends to be higher at older age.

3.3. Sensitivity and specificity of IgA [EBNA-1 + VCA p-18] ELISA

As an examination technique developed to diagnose KNF, the serological titles of IgA [EBNA-1 + VCAp-18] ELISA needs to be validated by comparing quantitatively with the gold standard (histopathology examination). A measuring instrument has high criterion validity if it is strongly correlated with standard gold gauge. The validity of criteria in this research is done two aspects, namely; validity and predictive validity. The one time validity assessment performed by calculating the sensitivity and specificity of the IgA [EBNA-1 + VCAp-18] serologic titers as a filter for KNF events (Table 3). The value of the proportion of positive subjects according to the gold standard (histopathology examination, positive KNF) identified as positive by the IgA [EBNA-1 + VCA p-18] ELISA titers or sensitivity which indicates the probability of this serologic titer to diagnose the subject as positively correct (Gerstman, 1998)(Last, 2001) are: TP / (TP + FN) = 95.7%. As for the value of the proportion of negative subjects according to the gold standard (histopathology examination, negative KNF) identified as negative by the IgA [EBNA-1 + VCA p-18] ELISA titers, or the specificity indicating this serological titer to correctly diagnose the subject as negative: TN / FP + TN = 77.1%

The combination of sensitivity and specificity of KNF serological diagnostic method with IgA [EBNA-1 + VCA p-18] ELISA was assessed to be seen on the Receiver Operating Characteristics (ROC)

curve. The value of the Under the Curve Area (AUC) is 86.4%, or it is means that the examination method is good value as a KNF diagnosis, since it is in the range 80.0-90.0% (Figure 1).

Predictive validity, prognostic validity, which refers to the suitability between IgA [EBNA-1 + VCA p-18] ELISA measurements and gold standard measurements (histopathology examination) is assessed by 'Positive Predictive Value (PPV)' and 'Value Predictive Negative '(NPV). The positive predictive value for IgA [EBNA-1 + VCA p-18] is the probability of the subject being positively identified by this serologic examination, and will actually be positive by the gold standards. As a screening tool, NPP IgA [EBNA-1 + VCA p-18] ELISA is: TP / TP + FP = 76.3%. Negative predictive value for IgA [EBNA-1 + VCA p-18] ELISA is the probability of the subject identified negatively by this serologic examination, would be completely negative by gold standards, with values: TN / TN + FN = 95.9%.

Calculation of accuracy of IgA examination [EBNA-1 + VCA p-18] ELISA in diagnosing KNF of: (TP + TN) / Total N) = 85.2%.

4. Discussion

EBV reactivation of the nasopharynx mucosal epithelium is an important momentum in nasopharyngeal carcinogenesis (Raab-Traub, 2002), and the detection of elevated antibody titers specific to EBV proves to be a reliable early diagnosis tool. Identification of IgA antibody titers [EBNA1 + VCA p-18] ELISA has good sensitivity and specificity for KNF screening in high-risk areas (Fachiroh, J., Paramita, DK., Hariwiyanto, B., Harijadi, A., 2006)(Paramita, D.K., Fachiroh J., Haryana, S.M. and Middeldorp, 2009). Our preliminary study detecting antibody titles IgA [EBNA1 + VCA p-18] ELISA serum samples of KNF patients and healthy individuals at risk in Semarang gained a picture of responses with higher reactivity, which is different from Makassar and Yogyakarta, so the question arises; whether the high antibody reactivity pattern against EBV in Semarang is related to specific localized risk factors for KNF. This study measured levels of IgA [EBNA1 + VCA p-18] ELISA titers in KNF and healthy at risk individuals.

Serological examination of IgA titers [EBNA-1 + VCA p-18] ELISA is in accordance with previous research standards and performed at the Biomolecular Laboratory of FK UGM (Fachiroh, J., Paramita, DK., Hariwiyanto, B., Harijadi, A., 2006)(Paramita, D.K., Fachiroh J., Haryana, S.M. and Middeldorp, 2009).

EBV humoral immunology-based studies play an important role in revealing the association of this virus with KNF. Diagnostic detection of antibodies relevant to EBV has been developed by several researchers, leading to the development of specific, easy and fast enzyme-linked immunosorbent assays (ELISAs), making it suitable for mass screening programs in high-risk populations. ELISA's diagnostic technique to EBV is facilitated by advances in monoclonal antibody technology, gene cloning, and expression of foreign proteins in cells and organisms, which facilitate differentiation of antibody profiles against individual EBV polypeptides (Gan, YY., Fones-Tan, A., Chan, SH., Tsao, SY., and Li, 1994)(Gan, YY., Fones-Tan, A., and Chan, 1996).

Various attempts were made to find the most sensitive and specific individual antibodies against the individual polypeptides to diagnose and monitor KNF patients. Finally, early antigen (EA) and nuclear antigen (EBNA) antigen (EBNA) -based antigen techniques were investigated based on recombinant antigens for EBV diagnosis (Farber, I., Wutzler, P., Wohlrabe, P., Wolf, H., Hinderer, W., and Sonneborn, 1993), and the combination of these tests may provide more objective data and is highly recommended as a marker of case detection KNF (Dardari, R., Hinderer, W., Lang, D., Benider, A., 2001).

The study of (Dardari, R., Hinderer, W., Lang, D., Benider, A., 2001) found that IgA-EA-p54 and -p138 antibodies (IgA-EA-p54 + 138) were diagnostic for 70% KNF detection, compared with IgA-VCA-p18 + 23 and IgA-EBNA-p72 which is having diagnostic limitation value, especially on the younger KNF sufferers. The combination of IgG-ZEBRA with IgA-EA-p54 + 138 increased the sensitivity of KNF detection to 95% of the entire KNF population. Furthermore, the (Fachiroh, J., Paramita, DK., Hariwiyanto, B., Harijadi, A., 2006) study has developed a combination of two synthetic peptides

representing the immuno dominant epitope of EBNA1 and VCA-p18 with the ELISA sandwich one-step technique, for the detection of IgB and IgB-reactive antibodies in KNF patients (EBV IgG / IgA ELISA), with 90.1% sensitivity and 85.4% specificity, a positive predictive value of 78.7% and a negative predictive value of 93.9%.

This study supported Fachiroh's opinion, and obtained sensitivity of IgA [EBNA-1 + VCA p-18] ELISA test of 95.7%, specificity 77.1%, with AUC value of ROC curve of 86.4%, which means that this method of examination is well worth detecting EBV infection and its involvement in KNF carcinogenesis. The positive predictive value and negative predictive value of IgA [EBNA-1 + VCA p-18] ELISA in this study was 76.3% and 95.9%, consecutively, and the calculation of accuracy in diagnosing KNF was 85.2%. Based on these data, it is concluded that the IgA [EBNA-1 + VCA p-18] ELISA test is potentially reliable as a KNF diagnostic marker, especially its ability to exclude negative results. In conclusion, the IgA-[EBNA1+VCA-p18] ELISA is a good method to discriminate NPC patients and their unaffected family members.

Conflict of interest

The authors declared no interest of conflicts.

Acknowledgement

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Figure and Table legends

Fig. 1. ROC curve sensitivity & specificity IgA [EBNA-1 + VCA p-18].

Table 1 Subject characteristic distribution on ELISA.

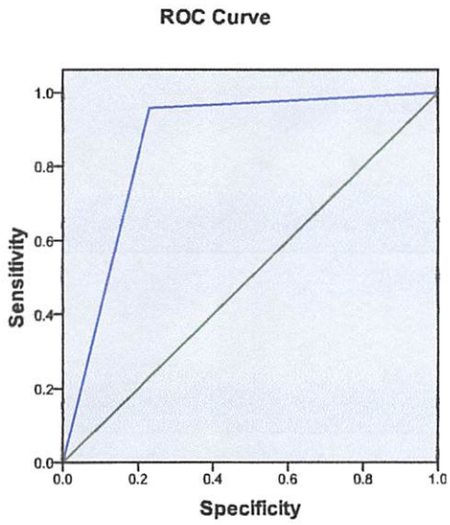
Table 2a Differences in IgA titers [EBNA-1 + VCA p-18] ELISA between case and control.

Table 2b Differences of IgA titles [EBNA-1 + VCA p-18] ELISA between male and female.

Table 2c Differences of IgA titles [EBNA-1 + VCA p-18] ELISA between young and old.

Table 3 One time validity & predictive validity for examination IgA [EBNA-1 + VCA p-18] ELISA.

Figures:



AUC=0.864, SE=0.037, *P*=0.000 (*Asymptotic* 95% CI = 0.791 to 0.937)

Fig. 1 ROC curve sensitivity & specificity IgA [EBNA-1 + VCA p-18]

Tables

Table 1. Subject characteristic distribution on ELISA

Characteristic	Group		Total f (%)	Differential Test/ *P* value
	Case (N=47) f (%)	Control (N=61) f (%)		
Gender				X^2=0.367
Male	35 (32.4%)	41 (38.0%)	76 (70.4%)	*P*=0.544*
Female	12 (11.1%)	20 (18.5%)	32 (29.6%)	
Total	47 (43.5%)	61 (56.5%)	108 (100.0%)	
Ages group				X^2=11.570
<20 th	1 (0.9%)	4 (3.7%)	5 (4.6%)	*P*=0.041**
20-29 th	3 (2.8%)	15 (13.9%)	18 (16.7%)	
30-39 th	10 (9.3%)	17 (15.7%)	27 (25.0%)	
40-49 th	19 (17.6%)	14 (13.0%)	33 (30.6%)	
50-59 th	7 (6.5%)	7 (6.5%)	14 (13.0%)	
≥60 th	7 (6.5%)	4 (3.7%)	11 (10.2%)	
Total	47 (43.5%)	61 (56.5%)	108 (100.0%)	

* *Continuity correction Chi-square test, P*>0,05 (insignificant)

***Pearson Chi-square, P*<0,05 (significant)

Table 2a. Differences in IgA titers [EBNA-1 + VCA p-18] ELISA between case and control.

IgA [EBNA-1+ VCA p-18] ELISA	Group		Total f (%)
	Case (N=47) f (%)	Control (N=61) f (%)	
Negative (<0.352)	2 (1.9%)	47 (43.5%)	49 (45.4%)
Positive (≥0.352)	45 (41.7%)	14 (13.0%)	59 (54.6%)
Total	47 (43.5%)	61 (56.5%)	108 (100.0%)

Continuity correction Chi-square test (X^2)=53,855, *P*=0,00 (significant)

Table 2b. Differences of IgA titles [EBNA-1 + VCA p-18] ELISA between male and female.

IgA [EBNA-1+ VCA p-18] ELISA	Group		Total f (%)
	♂ (N=47) f (%)	♀ (N=61) f (%)	
Negative (<0.352)	30 (27.8%)	19 (17.6%)	49 (45.4%)
Positive (≥0.352)	46 (42.6%)	13 (12.0%)	59 (54.6%)
Total	76 (70.4%)	32 (29.6%)	108 (100.0%)

Continuity correction Chi-square test (X^2)=2.84, *P*=0.092 (insignificant)

Table 2c Differences of IgA titles [EBNA-1 + VCA p-18] ELISA between young and old

IgA [EBNA-1+ VCA p-18] ELISA	Group		Total f (%)
	<40 th (N=50) f (%)	≥40 th (N=58) f (%)	
Negative (<0.352)	31 (28.7%)	18 (16.7%)	49 (45.4%)
Positive (≥0.352)	19 (17.6%)	40 (37.0%)	59 (54.6%)
Total	50 (46.3%)	58 (53.7%)	108 (100.0%)

Continuity correction Chi-square test (X^2)=9,176, *P*=0,002 (significant)

Table 3. One time validity and predictive validity for examination IgA [EBNA-1 + VCA p-18] ELISA.

IgA [EBNA-1+ VCA p-18] ELISA	Gold Standard (Histopathology Diagnosis)		Total
	Case (N=47) KNF (+)	Control (N=61) KNF (-)	
Positive (≥0.352)	45 (TP)	14 (FP)	59 (TP+FP)
Negative (<0.352)	2 (FN)	47 (TN)	49 (FN+TN)
Total	47 (TP+FN)	61 (FP+TN)	108 (Total N)

TP = *True Positive*; FP = *False Positive*; TN = *True Negative*; FN = *False Negative*; N = sampel; Sensitivity = 95.7%; Specifity= 77.1%; Predictive Positif Value = 76.3%; Predictive Negative Value= 95.9%; Accuration = 85.2%.

PP-22

Diagnostic value of IgA [EBNA1+VCA p-18] ELISA to discriminate nasopharyngeal cancer patients from their unaffected family members

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Introduction. Several studies have revealed the importance of detecting antibodies against specific EBV antigens, particularly IgA, that can be predictive or prognostic for nasopharyngeal cancer (NPC). Otherwise, it is still needed more data about the distinction of EBV sero-reactivity between the NPC and high risk unaffected individuals.
Aims. To evaluate the sensitivity and specivicity of IgA [EBNA1+VCA p-18] ELISA on histopathology diagnosis of NPC between NPC cases and high risk unaffected individuals (family members of NPC).
Methods. A case control study was conducted on 108 subjects, consisted of 47 NPC cases and 61 unaffected close family members as controls. Peripheral blood serum were tested for IgA [EBNA-1+VCAp-18] ELISA. Nasopharyngeal mucosal biopsies among NPC subjects were used as golden standard. The sensitivity and specificity, positive predictive value (PPV), and negative predictive value (NPV) of IgA-EBV ELISA were determined, by using CoV=0.352.
Result and discussion. The sensitivity and specificity of IgA [EBNA1+VCA p-18] ELISA were 95.7% and 77.1%, respectively. The combination of sensitivity and specificity for serological diagnostic method on NPC may be evaluated on ROC, that has area under curve (AUC) of 86.4%, or a good method for NPC diagnosis. The PPV and NPV of this test were 76.3% and 85.2%, respectively.
Conclusion. The IgA-[EBNA1+VCA-p18] ELISA is a good method to discriminate NPC patients from their unaffected family members.

Notes :

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POSTER DIPRINT

Arie Munandar, MD Dr. Cipto Mangunkusumo Hospital Jakarta	Profile of nasopharyngeal cancer who received therapy in Departement of Radiotherapy, Ciptomangunkusumo General Hospital January 2007–December 2011: special analysis on survival	PP-16
Endang Nuryadi, MD Dr. Cipto Mangunkusumo Hospital Jakarta	Comparison of radiotherapy response between conventional 2D technique with 2D, 3DCRT or brachytherapy booster in early stage of nasopharyngeal cancer treated at Dr. Cipto Mangunkusumo Hospital Jakarta, Indonesia	PP-41
Sri Mutya Sekarutami, MD Dr. Cipto Mangunkusumo Hospital Jakarta	Correlation study of pre-irradiation albumin level and hypoxia to radiation response in locally advanced nasopharyngeal carcinoma	PP-42
Nastiti Rahajeng, MD Dr. Cipto Mangunkusumo Hospital Jakarta	Response of radiation in nasopharyngeal carcinoma with locally advance stage in Radiotherapy Department Dr. Cipto Mangunkusumo National General Hospital from January 2007 to December 2011	PP-43

Poster Presentation
Translational Research on NPC

NAME	ABSTRACT TITLE	ABSTRACT NUMBER
Wan Lun Hsu Genomics Research Center, Academia Sinica, Taipei	Prediction of nasopharyngeal carcinoma risk by Epstein-Barr virus seromarkers and environmental co-factors: the gene-environment interaction study on nasopharyngeal carcinoma in Taiwan	PP-17
Sukri Rahman, MD Universitas Andalas, Padang, Indonesia	Non-viral risk factors for nasopharyngeal carcinoma in West Sumatra, Indonesia	PP-18
Coco Yin	New prototype VIDAS EBV IgA quick: performance on Chinese and Moroccan populations	PP-19
Dewi Syafriyetti Soeis Marzaini, MD, PhD RSCM Jakarta	The Expression of EBV-LMPI and VEGF as Predictors and Plasma EBV-DNA Levels as Early Marker of Distant Metastasis after Therapy in Nasopharyngeal Cancer	PP-20
Fari Daud, MD Maranatha Christian University	Non-viral risk factors of nasopharyngeal carcinoma in RSUD Sumedang, Indonesia	PP-21
Awal Prasetyo, MD Universitas Diponegoro, Semarang	Diagnostic value of IgA [EBNA1+VCA p-18] ELISA to discriminate nasopharyngeal cancer patients from their unaffected family members	PP-22
Dwi Hartati Universitas Gadjah Mada	Characteristics and factors influencing subjects refusal for blood samples retrieval: lesson from NPC case control study in Yogyakarta – Indonesia	PP-23

Certificate

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AS

SPEAKER

HAS SUCCESSFULLY COMPLETED THE

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Chairperson

SKP IDI No.049/IDI/WIL.DIY/SKP/III/2015 tanggal 30 Maret 2015

Participant: 16 SKP Speaker: 12 SKP Moderator: 4 SKP Committee: 2 SKP