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The use of nasopharyngeal electrodes in temporal lobe epilepsy

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The use of nasopharyngeal electrodes in temporal lobe epilepsy

Directed by Professor Kyoung Heo

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I will make efforts to make additional academic papers in the future through trial and error that I have experienced while writing my master's thesis.

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ABSTRACT

The use of nasopharyngeal electrodes in temporal lobe epilepsy

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Objective: To compare EEG recording with both anterior temporal (ATE) and nasopharyngeal electrode (NPE) (NPE recording) with EEG recording with only ATE (non-NPE recording) for the detection of interictal epileptiform discharges (IEDs) and bilateral independent IEDs in patients with temporal lobe epilepsy (TLE).
Methods: We retrospectively analyzed the initial EEGs which were recorded simultaneously with ATE and NPE in addition to 10-20 system electrodes in 229 patients with TLE. Two data sets of NPE and non-NPE recordings were reviewed independently by three interpreters with different experience. Discordant findings in interpretation among three interpreters were corrected by a consensus through elaborate review of EEG recordings, resulting in final results.
Results: Diagnostic sensitivity of IEDs in NPE/non-NPE recording was 60.3%/27.1% in beginner, 69.0%/49.8% in junior expert, and 74.2%/52.0% in senior expert. In the final results, IEDs were detected in 76.4% with NPE compared to 55.5% with non-NPE ($p < 0.001$). Bilateral IEDs were found in 26 of 127 EEGs with IEDs with non-NPE and 60 of 175 EEGs with IEDs with NPE ($p = 0.006$). Diagnostic yield of NPE for the detection of IEDs was significantly increased in mesial and non-lesional TLEs. Agreement degree for the detection of IEDs among three interpreters in NPE was higher than that in non-NPE (κappa score 0.703 versus 0.536).
Conclusion: EEG recording by using NPE in combination with the standard electrodes and ATE may improve the sensitivity and the level of agreement in the detection of IEDs in TLE regardless of different experience of EEG interpretation. Furthermore, application of NPE could enhance the detection of bilateral IEDs.

Key words: nasopharyngeal electrodes, anterior temporal electrodes, temporal lobe epilepsy, 10-20 electrode system

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I INTRODUCTION

Since 1958, the international 10-20 electrode positioning system was introduced,[1] it has been played the role as standardized EEG guideline in epilepsy centers worldwide.[2] However, although the conventional 10-20 system of electrode placement has been generally accepted in clinical epilepsy practice, many epilepsy experts have pointed out that it does not thoroughly measure the entire temporal lobe, especially mesio-basal aspects of the temporal lobes.[3-5]

In order to overcome the limitation of conventional 10-20 electrode positioning system, several additional electrodes have been introduced, such as anterior temporal electrode (ATE),[6,7] anterior cheek electrode,[8] mini-sphenoidal electrode,[9] nasopharyngeal electrode (NPE),[10] sphenoidal electrode (SPE),[11] inferior temporal electrode,[12] and foramen ovale electrode (FOE).[13]

SPE and FOE have been accepted as reliable methods for evaluation of the mesio-basal temporal lobe epilepsy (TLE) on account of the tendency of definitively larger amplitude signals than all other types of additional electrodes.[14-21] However, they have been difficult to commonly be used in a routine EEG recording because those two electrodes are characterized by invasive and elaborate procedure.[13,22,23]

In these practical reasons, ATE are frequently used in most laboratories.[5,6,24,25] However, several studies have suggested that the use of NPE in combination with the standard electrodes with or without ATE may be helpful in the detection of IEDs in a significant number of patients with no IEDs on the scalp electrodes, or in increasing the number of IEDs.[26-31] Recent study for seven patients with TLE, which was implemented simultaneously by subdural electrodes, indicated that spikes only recorded by NPE had mesio-basal temporal, while ATE spikes had lateral temporal distribution.[31] EEG analysis based on dipole modeling in TLE revealed electrical heterogeneity dependent on whether epileptic zone was located at mesial or lateral temporal lobe.[32,33] Therefore, the use of NPE may improve the detection rates of IEDs in some patients with TLE.

Previous studies which were performed with conventional 10-20 electrode system without additional electrodes in adult patients[34] or with 10-20 electrode system and ATE in adult and pediatric patients,[35] have reported that the agreement of EEG interpretation among the interobservers were found to be only moderate. The amplitudes of IEDs detected in NPE may be frequently higher in patients with TLE than those of IEDs in temporal electrodes of 10-20 electrode positioning system and ATE. The use of NPE may facilitate the detection of IEDs. Especially, for less EEG-experienced neurologists, the use of NPE may increase the sensitivity in detection of IEDs in patients with TLE, which may increase the agreement of the detection of IEDs with EEG experts. In this report we conducted a comparative study between EEG recordings with both NPE and ATE (NPE recording) and EEG recordings with only ATE (non-NPE recording) in combination with 10-20 electrode system electrodes for the same patients, and investigated whether applying NPE have additionally informative and complementary function to interpret scalp EEG. Also, we investigated the difference in detection of IEDs according to the experience degree of EEG interpretation.

II MATERIALS AND METHODS

1. Subjects

The patients with TLE were selected in epilepsy patients who had consecutively visited the outpatient epilepsy clinic of Severance Hospital by a physician (K. Heo) from March 2010 to March 2016. The diagnosis of TLE was determined by the correlation of ictal semiology, EEG, and MRI features. Patients whose initial EEGs included ictal activity were excluded. Enrolled patients were grouped into non-lesional TLE and lesional TLEs (mesial TLE, lateral TLE, and undetermined TLE according to lesion location) by visual analysis of brain MRI. In classification as mesial or lateral TLE in lesional TLE, collateral sulcus was selected as a boundary.[36] When patients had the lesion included both sides of the collateral sulcus, or the dual lesions present in both sides of the collateral sulcus in temporal lobe, they were classified as having undetermined TLE.

We analyzed EEGs which were simultaneously performed with ATE and NPE in combination with electrodes of 10-20 electrode positioning system as the initial evaluation in Severance Hospital. This study was approved by the Institutional Review Board of the Severance Hospital.

2. EEG

NPE was used with the product of GRASS technologies, which is insulated and flexible wire terminating in a 3-mm gold plated ball. EEG recordings were obtained with a 57-channel AS40-PLUS Amplifier System, GRASS® Comet-PLUS® EEG. EEGs were recorded for about 40 minutes with 200 Hz sampling rate, were filtered at 1-70 Hz, and reviewed usually at 7 μv/mm and 26 mm/s. We used the four commonly used montages with or without ATE in combination with electrodes of 10-20 electrode positioning system, which consisted of two bipolar montages (longitudinal and transverse) and two monopolar montages (A1/A2 and Cz references, respectively). Additionally, two mixed bipolar and monopolar montages, and one bipolar montage were used with the combination of ATE and NPE for EEG analysis of NPE recording. The same manners of montages without NPE were used for EEG analysis of non-NPE recording (Figure 1). EKG was checked in all montages.

Common four montages				Three montages Combination electrodes (ATE + NPE)			Three montages Only ATE		
Fp1-F7	Fp1-A1	Fp1-Fp2	Fp1-Cz	T3-F7	C3-T3	Fp1-F7	T3-F7	C3-T3	Fp1-F7
F7-T3	F3-A1	T1-F7	F3-Cz	F7-NP1	T3-Np1	F7-Np1	F7-T1	T3-T1	F7-T1
F3-T5	C3-A1	F7-F3	C3-Cz	NP1-NP2	Np1-Np2	Np1-T3	T1-T2	T1-T2	T1-T3
T5-O1	P3-A1	F3-Fz	P3-Cz	NP2-F8	Np2-T4	T3-T5	T2-F8	T2-T4	T3-T5
Fp2-F8	O1-A1	Fz-F4	O1-Cz	F8-T4	T4-C4	T5-O1	F8-T4	T4-C4	T5-O1
F8-T4	Fp2-A2	F4-F8	Fp2-Cz	Fp1-F7	C4-Cz	O1-O2	Fp1-F7	C4-Cz	O1-O2
T4-T6	F4-A2	F8-T2	F4-Cz	F7-Np1	Cz-C3	O2-T6	F7-T1	Cz-C3	O2-T6
T6-O2	C4-A2	A1-T3	C4-Cz	Np1-T3	Fp1-Cz	T6-T4	T1-T3	Fp1-Cz	T6-T4
Fp1-F3	P4-A2	T3-C3	P4-Cz	T3-T5	F7-Cz	T4-Np2	T3-T5	F7-Cz	T4-T2
F3-C3	O2-A2	C3-Cz	O2-Cz	T5-O1	T1-Cz	Np2-F8	T5-O1	T1-Cz	T2-F8
C3-P3	F7-A1	Cz-C4	F7-Cz	Fp2-F8	Np1-Cz	F8-Fp2	Fp2-F8	T3-Cz	F8-Fp2
P3-O1	T1-A1	C4-T4	T1-Cz	F8-Np2	T3-Cz	Fp1-F3	F8-T2	T5-Cz	Fp1-F3
Fp2-F4	T3-O1	T4-A2	A1-Cz	Np2-T4	T5-Cz	F3-C3	T2-T4	O1-Cz	F3-C3
F4-C4	T5-A1	T5-P3	T3-Cz	T4-T6	O1-Cz	C3-P3	T4-T6	Fp2-Cz	C3-P3
C4-P4	F8-A2	P3-Pz	T5-Cz	T6-O2	Fp2-Cz	P3-O1	T6-O2	F8-Cz	P3-O1
P4-O2	T2-A2	Pz-P4	F8-Cz	Np1-Cz	F8-Cz	Fp2-F4	T1-Cz	T2-Cz	Fp2-F4
Fz-Cz	T4-A2	P4-P6	T2-Cz	Np2-Cz	T2-Cz	F4-C4	T2-Cz	T4-Cz	F4-C4
T1-T2	T6-A2	O1-O2	A2-Cz	T1-Cz	Np2-Cz	C4-P4	A1-Cz	T6-Cz	C4-P4
A1-A2	Fz-A1	T1-Cz	T4-Cz	T2-Cz	T4-Cz	P4-O2	A2-Cz	O2-Cz	P4-O2
	Cz-A1	T2-Cz	T6-Cz	A1-Cz	T6-Cz	T1-T2			T1-T2
	Pz-A1			A2-Cz	O2-Cz	Np1-Np2			

Figure 1. The montages used in interpretation of NPE recording and non-NPE recording. The montages used in interpretation of NPE recording consisted of the combination of NPE and ATE, while those in interpretation of non-NPE recording were made by ATE only. EEG interpretation in both NPE and non-NPE recording shared the four montages based on international 10-20 electrode system.

3. Analysis

Two sets of EEG data were arranged for EEG analyses of NPE and non-NPE recordings, respectively. The order of EEGs in two sets of EEG data was different to prevent communication between two sets of EEG data. The patient's information which includes hospital number, name of patients, previous EEG results, and brain MRI finding, was blinded to three interpreters. Three neurologists interpreted two sets of 229 EEG recordings (229 patients) retrospectively and independently. Three EEG interpreters consisted of a senior neurologist (K. Heo) (senior) and a junior neurologist (K. H. Cho) (junior) who had experienced clinical epilepsy practice including EEG interpretation for 27 and half years and for 5 and half years, respectively, and a junior neurologist (S. H. Yim) (beginner) who was being trained for 6 months as epilepsy fellow.

IEDs were defined as spike, sharp wave, polyspike, or spike wave discharges. They are typically <200 ms in duration and distinguished by their morphology and/or amplitude from normal EEG background. Normal EEG variants such as small sharp spikes and wicket spikes were not considered IEDs. The interpreters underwent no specific training or preparation for the study. Conservative interpretation was warranted whenever doubt existed. If IEDs were detected, laterality of IEDs (unilateral and bilateral independent) and electrodes(s) showing maximum amplitude of IEDs were investigated. The amplitude of IEDs was estimated visually as peak to peak in Cz reference montage. When maximum amplitude of IEDs was detected consistently at specific electrode(s) in an EEG recording, specific electrode(s) were regarded as electrode(s) showing maximum amplitude of IEDs. When maximum amplitude of IEDs was detected independently at different electrode(s), both different electrode(s) were regarded as electrode(s) showing maximum amplitude of IEDs. Electrode(s) showing maximum amplitude of IEDs was investigated separately on each side in EEGs with bilateral independent IEDs. Also, the number of IEDs was counted and classified to ≥10 times and <10 times. In EEGs with bilateral independent IEDs, the number of IEDs on each side was investigated separately and duplicated number was added to the denominator when the proportion of ≥10 times or <10 times was calculated, which was somewhat arbitrary. After individual interpretation, discordant interpretation findings for the presence of IEDs and bilateral IEDs among three interpreters were corrected by a consensus through elaborate review of EEG recordings, resulting in final results. However, the electrode(s) showing maximum amplitude of IEDs and the number of IEDs were determined by EEG interpretation of senior or of others in some EEGs which were false negative for IED detection in EEG interpretation of senior.

4. Statistically Analysis

Statistically analysis was performed for comparison of diagnostic performances using the generalized estimating equation (GEE). The correlation of EEG interpretation between NPE and non-NPE recordings according to each EEG analysts was analyzed by using McNemar’s test. And, the laterality of detected IEDs between NPE and non-NPE was analyzed by using proportion test. A p value of 0.05 was considered significant. The agreements of EEG interpretations between NPE and non-NPE recordings were evaluated by Fless's kappa score, and the agreements of EEG analysis among three EEG interpreters were estimated by Cohen's kappa score. Comparisons between NPE and non-NPE recordings about agreement of EEG interpretations were performed with kappa comparisons. The adjusted p-value was confirmed using the Bonferroni correction. R version 3.4.4 (The R Foundation for Statistical Computing, Vienna, Austria) and SAS (version 9.4, SAS Inc., Cary, NC, USA) were used.

III RESULTS

1. Demographics

This study included 229 patients (229 EEGs). Their age ranged from 13 to 88 years (mean 45.0 years old) at the initial EEG recordings, and mean age of onset was 34.0 years old. Among the 229 patients included in the study, MRI was not remarkable finding in 64 patients (27.9%). Hippocampal sclerosis (n = 43, 18.1%) was most frequently enrolled pathology in types of MRI lesion, followed by amygdala enlargement (n = 42, 17.6%), cerebromalacia (n = 36, 15.1%), vascular malformation (n = 18, 7.6%), brain tumor (n = 14, 5.9%), focal cortical dysplasia (n = 11, 4.6%), dual pathology (n = 9, 3.9%) and tuberous sclerosis (n = 3, 1.3%). Locational types of MRI lesion were grouped into mesial temporal (n = 107/165, 64.8%), lateral temporal (n = 38/165, 23.0%), and undetermined temporal (n = 20/165, 12.1%). Dual pathology (n = 9) all belonged to undetermined temporal. Dual pathology consisted of hippocampal sclerosis associated with other lesions (n = 7) and amygdala enlargement with other lesions (n = 2).

2. EEG interpretation among three interpreters

In patients whose non-NPE recordings were interpreted as having IEDs by each interpreter, IEDs were always detected in interpretation of their NPE recordings by each interpreter. Regardless of experience for EEG interpretations, the diagnostic sensitivities of IEDs in EEG interpretation with NPE were significantly superior to those in EEG interpretation with non-NPE in all three interpreters ($p < 0.001$). Diagnostic sensitivity of beginner in NPE (138/229, 60.3%) was higher than that in non-NPE recording (62/229, 27.1%) ($p < 0.001$). Diagnostic sensitivity of junior in NPE (158/229, 69.0%) was higher than that in non-NPE recording (114/229, 49.8%) ($p < 0.001$). Diagnostic sensitivity of senior in NPE (170/229, 74.2%) was also higher than that in non-NPE recording (119/229, 52.0%) ($p < 0.001$).

Table 1. Comparison among three interpreters in EEG interpretation with NPE and non-NPE recordings

	Method	Presence of IEDs (Sensitivity %)	Laterality of IEDs		The number of IEDs*	
			Unilateral	Bilateral	1< IEDs < 10	IEDs ≥10
EEG beginner	NPE	138/229 (60.3%)	115	23	99/252 (39.3%)	62/252 (24.6%)
	Non-NPE	62/229 (27.1%)	56	6	53/235 (22.6%)	15/235 (6.4%)
	P value	< 0.001	< 0.001		< 0.001	< 0.001
Junior EEG specialist	NPE	158/229 (69.0%)	108	50	104/279 (37.3%)	104/279 (37.3%)
	Non-NPE	114/229 (49.8%)	93	21	76/250 (30.4%)	59/250 (23.6%)
	P value	< 0.001	< 0.001		0.058	< 0.001
Senior EEG specialist	NPE	170/229 (74.2%)	114	56	83/285 (29.1%)	143/285 (50.2%)
	Non-NPE	119/229 (52.0%)	92	27	52/256 (20.3%)	94/256 (36.7%)
	P value	< 0.001	< 0.001		0.012	0.001
Consensus interpretation	NPE	175/229 (76.4%)	115	60	91/289 (31.5%)	144/289 (49.8%)
	Non-NPE	127/229 (55.5%)	101	26	58/255 (22.7%)	95/255 (37.3%)
	P value	< 0.001	< 0.001		0.014	0.002

The number of IEDs* indicate that in EEGs with bilateral independent IEDs, the number of IEDs on each side was investigated separately and duplicated number was added to the denominator.

Regardless of experience for EEG interpretations, the detection rates of bilateral IEDs with NPE recording were higher to those of bilateral IEDs with non-NPE recording in all three interpreters (10.0 % versus 2.6% in beginner, $p < 0.001$; 21.8% versus 9.2% in junior, $p < 0.001$; 24.5% versus 11.8% in senior, $p < 0.001$). Also, in EEGs with IEDs, the proportions of bilateral IEDs were higher in NPE recording than in non-NPE recording (16.7% versus 9.6% in beginner, $p = 0.139$; 31.6% versus 18.4% in junior, $p < 0.01$; and 32.9% versus 22.7% in senior, $p < 0.003$ respectively).
The proportions of EEGs with IEDs < 10 of overall EEGs (duplicated in EEGs with bilateral IEDs) were higher in NPE recording than in non-NPE recording in the interpretation by beginner and senior (39.3% versus 22.6% in beginner, $p < 0.001$; 29.1% versus 20.3% in senior $p = 0.012$) but not in the interpretation by junior (37.3% versus 30.4% in junior, $p = 0.058$). The proportions of EEGs with IEDs ≥ 10 were higher in NPE recording than in non-NPE recording in all interpreters (24.6% versus 6.4% in beginner, $p < 0.001$; 37.3% versus 23.6% in junior, $p < 0.001$; and 50.2% versus 36.7% in senior, $p = 0.001$). In EEGs with IEDs, the proportions of IEDs ≥ 10 were higher in the interpretation of NPE than non-NPE recordings by beginner but not by junior and senior (38.5% versus 20.8% in beginner, $p = 0.012$; 50.0% versus 43.7% in junior, $p = 0.152$; and 63.3% versus 64.4% in senior, $p = 0.543$).

3. Consensus EEG interpretation in NPE and non-NPE recordings

False positive rates of each three interpreters in the detection of IEDs revealed 3.1% and 2.3% in beginner; 0% and 3.4% in junior; 0% and 0% in senior, respectively. Diagnostic sensitivity in NPE recording (76.4%) was superior in identification of IEDs than that in non-NPE recording (55.5%) ($p < 0.0001$). EEG interpretation with NPE recording provided a further yield of 20.9% in the detection rate of IEDs in overall EEGs. IEDs were identified with NPE recording in 48 patients (47.1%) of 102 patients in whom IEDs were not detected in EEG interpretation with non-NPE recording. The detection rate of bilateral IEDs in NPE recording were higher than that of bilateral IEDs in non-NPE recording (26.2% and 11.4%, $p < 0.001$). Also, in EEGs with IEDs, the proportion of bilateral IEDs was higher in NPE recording than in non-NPE recording (34.3% and 20.5%, $p = 0.006$). The proportions of EEGs with IEDs < 10 or ≥ 10 of overall EEGs (duplicated in EEGs with bilateral IEDs) with NPE recording were higher than those with non-NPE recording (31.5% versus 22.7%, $p = 0.001$: and 49.8% versus 37.3%, $p = 0.002$, respectively). In EEGs with IEDs, the proportion of IEDs ≥ 10 were similar between NPE and non-NPE recording recordings (61.3% versus 62.1%, $p = 0.522$). We demonstrated several examples with discrepancy in detection of IEDs between NPE and non-NPE recordings (Figures 2a-2g).

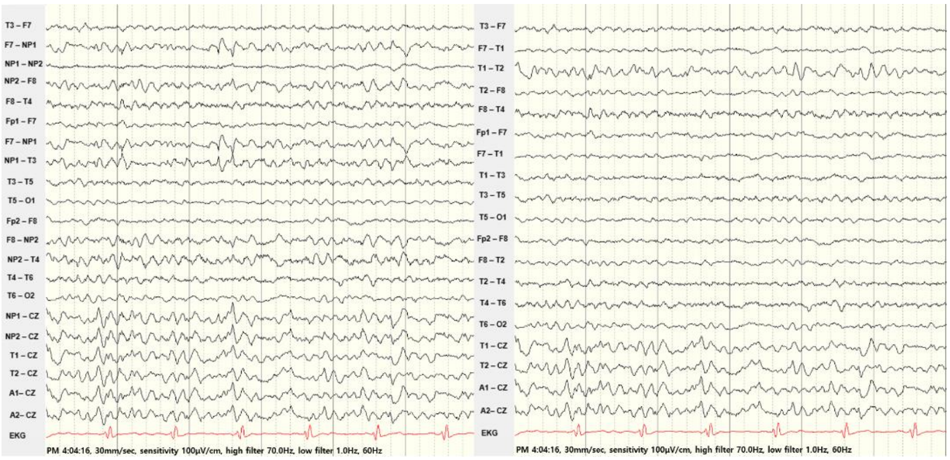

Figure 2a. 48-year-old man with the left hippocampal sclerosis. IEDs were definitely seen on NPE recording (left) but less sharp and less distinct from the background activity on other electrodes. Therefore, these discharges were not regarded as IEDs in EEG interpretation with non-NPE recording by all three interpreters (right).

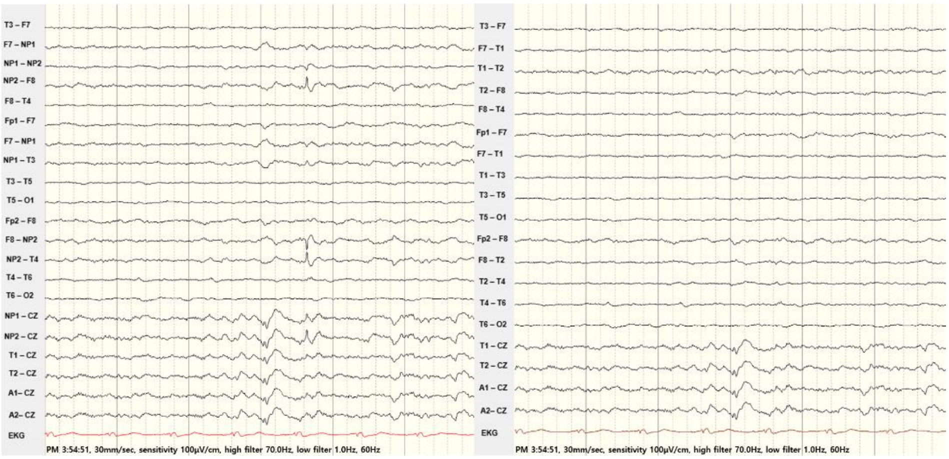

Figure 2b. 72-year-old man with the right amydala enlargement. IED is definitively seen only on NPE (left) with no evidence of IED on other electrodes (right). This non-NPE recording was not regarded as having IEDs by all three interpreters.

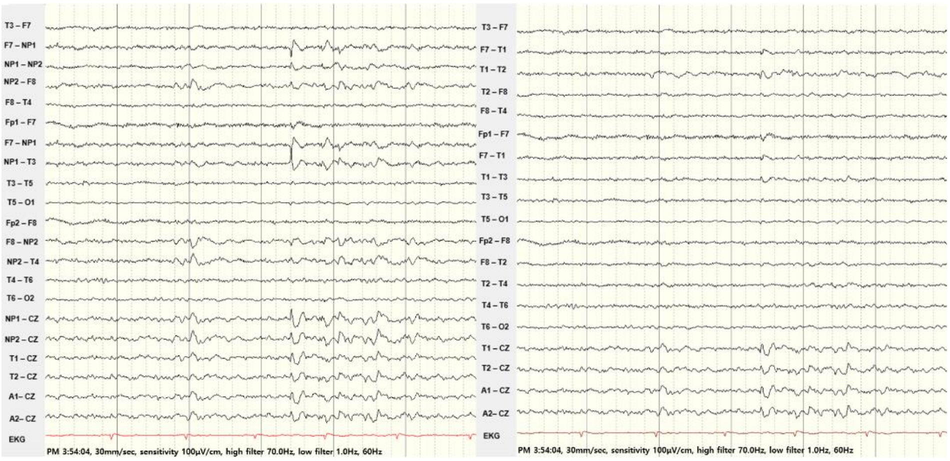

Figure 2c. 53-year-old man with the left amygdala enlargement. Beginner could identify IEDs in NPE recording (left) but not IEDs in non-NPE recording (right). Both junior and senior were able to identify IEDs in both EEG recordings.

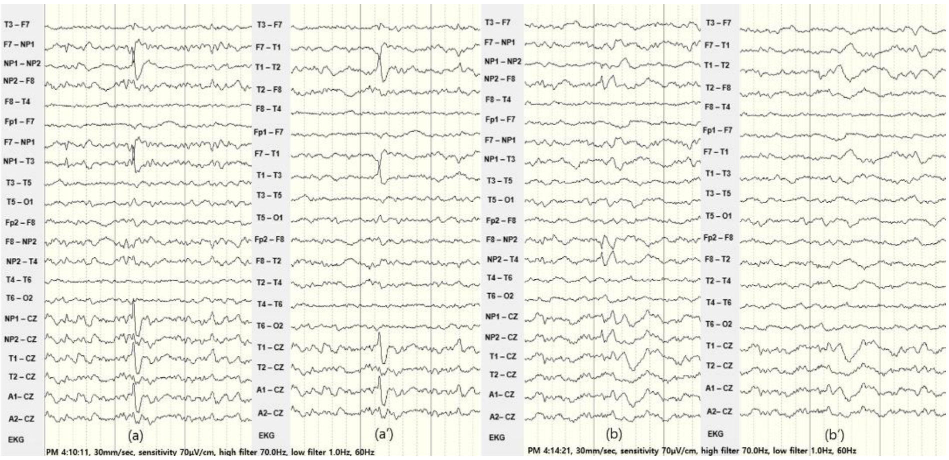

Figure 2d. 44-year-old man with the left hippocampal sclerosis. Both NPE (a) and non-NPE (a´) recordings shows IED in the left temporal region (NP1 maximum). Also, NPE recording (b) shows right IED clearly seen at NP2 only (bilateral independent IEDs). On the other hand, non-NPE recording (b´) reveals no definitive IED in the right temporal region.

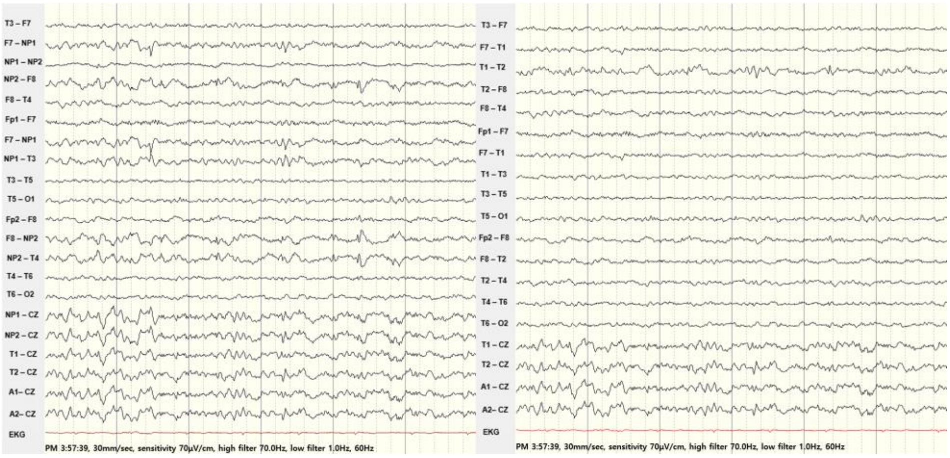

Figure 2e. 51-year-old man with the right hippocampal sclerosis. NPE recording (left) shows bilateral independent IEDs in the temporal region (NP2 or NP1 maximum) which were identified by all interpreters. Although both junior and beginner were not able to identify IEDs in non-NPE recording, IEDs in the right temporal region could be identified by senior.

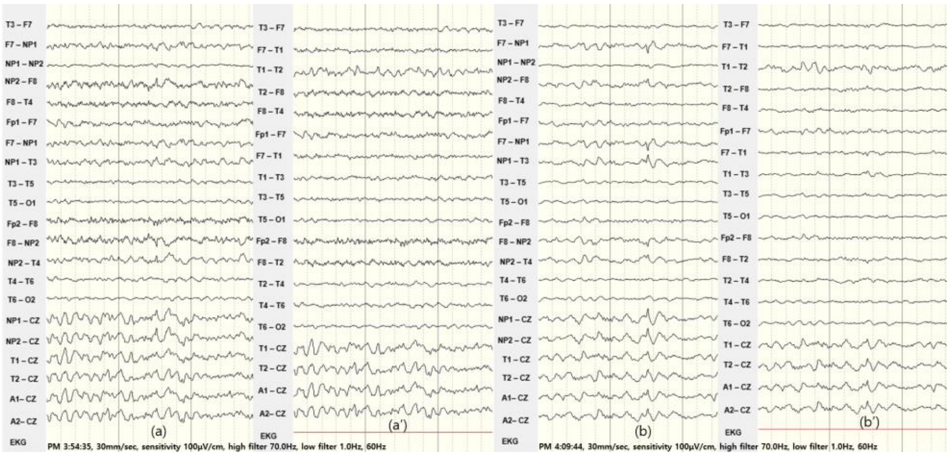

Figure 2f. 43-year-old man with the right hippocampal sclerosis. NPE recordings (a and b) show bilateral independent IEDs. On the other hand, in non-NPE recordings (a´ and b´), these discharges were less sharp and less distinct from the background activity and were not regarded as IEDs by all three interpreters.

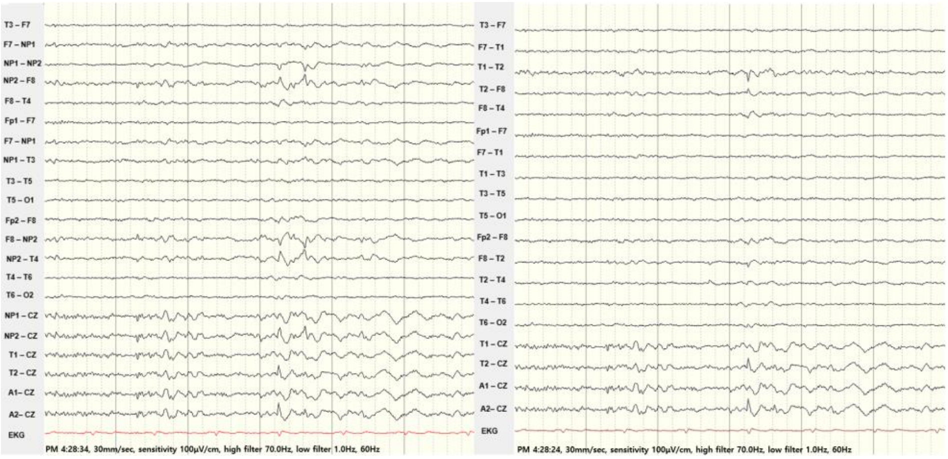

Figure 2g. 49-year-old woman with the cerebral encephalomalacia in the right temporal region. Two IEDs were detected in the right temporal region on NPE recording (left), but only one IED (T2 maximum) was identified on non-NPE recording (right).

4. Electrodes showing the maximum amplitude of IEDs

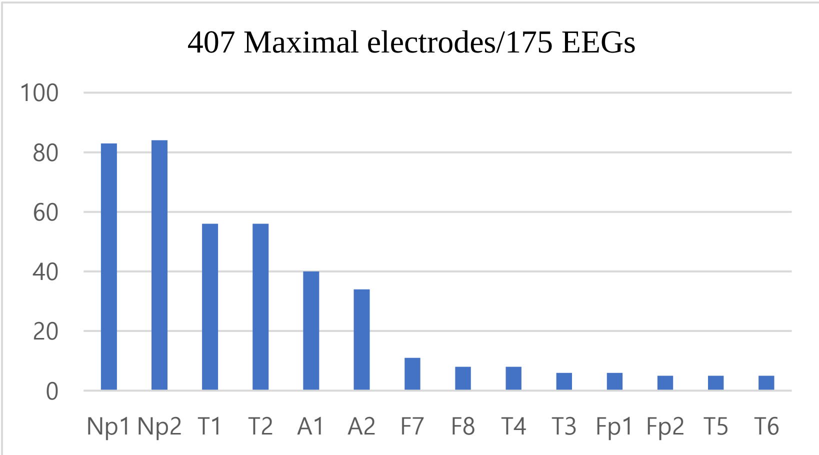

Figure 3. Electrodes showing the maximum amplitude of IEDs Because the location showing the maximum amplitude of IEDs was multiple in 103 EEG recordings, plural location of IEDs were allowed in this result (n = 407). Electrodes of maximum IEDs were as the order of frequency, NPE (n = 167 [41.0%]; NP1: 83, NP2: 84), ATE (n = 112 [27.5%], T1: 56, T2: 56), ear

electrodes (n = 74 [18.2%]; A1: 40, A2: 34), frontotemporal temporal electrodes (n = 19 [4.7%]; F7: 11, F8: 8), middle temporal electrodes (n = 14 [3.4%]; T3: 6, T4: 8), posterior temporal electrodes (n = 10 [2.5%]; T5: 5, T6: 5), and frontopolar electrodes (n = 11 [2.7%]; Fp1: 6, Fp2: 5).

5. Agreement degree of EEG interpretation

The agreement of the detection of IEDs among three interpreters in EEG interpretation with non-NPE recording revealed moderate degree (Fleiss's kappa, κ: 0.536) although it showed substantial degree (Cohen's kappa, κ: 0.779) between junior and senior. On the other hand, the agreement among three interpreters in EEG interpretation with NPE recording improved to substantial degree (Fleiss's kappa, κ: 0.717). EEG interpretation with NPE by beginner significantly increased the degree of agreement with both junior and senior (Cohen's kappa, κ: 0.453 to 0.717 with junior, $p < 0.001$; κ: 0.479 to 0.678 with senior, $p = 0.014$). On the other hand, agreement degree of EEG interpretation between two EEG specialists did not show meaningful change with application of NPE (kappa comparison adjusted by Bonferroni correction, $p = 0.999$).

Table 2. Comparison between EEG interpretation with NPE and non-NPE recordings in consensus EEG interpretation

Method	Fleiss's Kappa		Cohen's kappa		
			Beginner VS Junior	Beginner VS Senior	Junior VS Senior
NPE	0.703		0.717	0.678	0.776
Non-NPE	0.536		0.453	0.479	0.779
		Raw p value	< 0.001	0.005	0.968
		Adjusted p value	< 0.001	0.014	0.999

K score range of 0 to 0.2 are considered to be slight agreement, 0.2 to 0.4 fair agreement, 0.4 to 0.6 moderate agreement, 0.6 to 0.8 substantial agreement, and 0.8 to 1.0 almost perfect agreement.[37]

6. According to pathological types and location of brain MRI lesion, diagnostic sensitivity of NPE and non-NPE recordings

The detection rate of IEDs in mesial TLE was significantly higher by using NPE recording than by using non-NPE recording (82.2% versus 62.6%, p <

0.001). Also, in non-lesional TLE and overall lateral TLE, the detection rates of IEDs by using NPE recording were significantly higher than those by using non-NPE recording (68.8% versus 42.2%, $p < 0.001$; and 76.3% versus 63.2%, $p = 0.016$, respectively). NPE recording showed significantly higher diagnostic sensitivity in the detection of IEDs than non-NPE recording in isolated amygdala enlargement (87.5% versus 67.5%, $p = 0.002$) and hippocampal sclerosis (91.7% versus 63.9%, $p = 0.001$). NPE in undetermined TLE also indicated a higher diagnostic performance rather than that by non-NPE (70.0% versus 45.0%, $p = 0.009$).

Table 3. According to pathological types and locational type of brain MRI lesion, comparison of diagnostic sensitivity between NPE and non-NPE recordings

Location	Type of pathology	Method	P. IED	A. IED	Sensitivity (%) (95% CI)	*Types of Location p value*	*Types of pathology p* value
Non-lesional (N = 64)		NPE Non-NPE	44 27	20 37	68.8 (57.4-80.1) 42.2 (30.1-54.3)	< 0.001	
Mesial TLE (N = 107)	HS (n = 36)	NP Non-NPE	33 23	3 13	91.7 (82.6-100.0) 63.9 (48.2-79.6)	< 0.001	0.001
	AE (n = 40)	NPE Non-NPE	35 27	5 13	87.5 (77.3-97.8) 67.5 (52.9-82.0)		0.002
	AVM (n = 8)	NPE Non-NPE	3 3	5 5	37.5 (20.8-54.3) 37.5 (20.8-54.3)		0.114
	BT (n = 10)	NPE Non-NPE	7 6	3 4	70.0 (41.6-98.4) 60.0 (32.7-87.3)		0.693
	FCD (n = 6)	NPE Non-NPE	5 4	1 2	83.3 (61.8-100.0) 62.5 (43.3-75.2)		0.563
	CM (n = 6)	NPE Non-NPE	4 4	2 2	62.5 (43.3-75.2) 62.5 (43.3-75.2)		0.127
	MISC (n = 1)	NPE Non-NPE	1 0	0 1	100.0 (50.1-100.0) 0 (0.0-40.1)		0.658
Lateral TLE (N=38)	CM (n = 21)	NPE Non-NPE	16 14	5 7	76.1 (54.2-89.4) 66.7 (47.2-81.7)	0.016	0.5424
	AVM (n = 7)	NPE Non-NPE	5 4	2 3	71.4 (47.8-95.1) 57.1 (31.2-83.4)		0.3583
	BT (n = 3)	NPE Non-NPE	2 1	1 2	66.7 (44.5-85.3) 33.3 (20.5-70.1)		0.4721
	FCD (n = 2)	NPE Non-NPE	1 1	1 1	50.0 (35.5-76.7) 50.0 (35.5-76.7)		0.9999
	MISC (n = 5)	NPE Non-NPE	5 5	0 0	100.0 (75.1-100.0) 100.0 (75.1-100.0)		0.9999
Undetermined TLE (n = 20) Dual pathology (n=9) included		NPE Non-NPE	14 9	6 11	70.0 (49.9-90.1) 45.0 (23.2-66.8)	0.009	

Abbreviations: P. IED = Present of IED, A. IED = absent IED, HS = hippocampal sclerosis, AE = amygdala enlargement, AVM = arteriovenous malformation, BT = brain tumor, FCD = focal cortical dysplasia, CM = Cerebral malasia, MISC = miscellaneous

7. Clinical characteristics of exclusively detected IEDs in NPE recordings

In 48 patients with EEGs in which IEDs were detected only in NPE recording, Locational types of MRI lesion in which IEDs were detected only in NPE recording showed in this following order; mesial TLE (n = 23), lateral TLE (n = 6) and undetermined TLE (n = 3). (Proportion test by using Fischer's Exact test, p = 0.69). Brain MRI revealed in this following order; non-lesional TLE (n = 16), hippocampal sclerosis (n = 11), amygdala enlargement (n = 8), cavernous malformation (n = 3), cerebromalacia (n = 3), dual pathology (n = 3), and focal cortical dysplasia (n = 2).

IV DISCUSSION

This study suggests that EEG recording by using NPE in combination with the standard electrodes and ATE may increase the detection rate of IEDs in patients with TLE and may facilitate the detection of IEDs in interpreters with less experience of EEG interpretation. Furthermore, the presence of bilateral IEDs was more frequently found in NPE recording, which may give clinical significance in the determination of epileptogenic focus.

Theoretically, NPE may be more effective in the detection of IEDs occurring in mesial temporal region than lateral temporal electrodes because of anatomical location of NPE. Furthermore, thickness of skull basal bone (approximately < 1.0 mm) is tendency to be much smaller than that of lateral temporal bone (> 3.0 mm).[38,39] Furthermore, previous studies reported that two patterns of spike voltage topography, termed type 1 and type 2, were commonly observed in patients with TLE.[40,41] Type 1 spikes had a inferio-lateral negative field with a maximum on supplementary subtemporal electrodes, and a positive maximum on electrodes around the vertex. Type 2 spikes had a more lateral negative field and a positive maximum that was found on the opposite side of the head. Subsequent investigation with dipole modeling demonstrated that the horizontal and radial nature of type 2 spike dipoles suggested sources in lateral temporal cortex, whereas the more vertical and tangential orientation of type 1 spike dipoles suggested inferior and basal temporal cortex sources.[33] Therefore, NPE which are inserted into nostril could be relatively easy to detect IEDs, especially from inferior and basal temporal region than lateral temporal electrodes of international 10-20 system and ATE. A recent study compared NPE, cheek electrodes, and ATE for the detection yield and localization of IEDs in seven patients with TLE evaluated with simultaneous recording by subdural electrodes, and indicated that NPE can increase EEG spikes detection rates, and spikes only recorded by NPE had mesio-basal temporal, while ATE spikes had lateral temporal distribution[31]. In our study, NPE recording showed a significantly higher diagnostic sensitivity in the detection of IEDs than non-NPE in mesial TLE which was classified by lesion location. Also, NPE recording could significantly help to identify IEDs more than non-NPE recording in non-lesional TLE. This finding may be supported by studies that have found IEDs more frequently in mesial temporal lobe than in lateral temporal lobe on intracranial EEG recordings for non-lesional TLE patients.[42,43] Amygdala enlargement has been still unclear in its pathology and pathophysiology, it may be not uncommon MRI finding in patients with TLE and particularly, a later age of seizure onset.[44,45] Although its diagnosis was done by visual inspection in our study, NPE recording showed significantly higher sensitivity in the detection of IEDs than non-NPE because it could suggest mesial temporal origin of epilepsy.

In clinical practice, whether NPE increase the yield in addition to surface electrodes has been subject of debate. Several previous studies have shown that NPE can give some additive diagnostic yield in addition to the scalp electrodes. Crucial abnormalities were shown by NPE recording when there were few or no concomitant surface signs in 30 records in 28 patients (30 of 838 EEGs, 3.6%).[29] In a study which investigated the ability of NPE to record IEDs in a total of 121 patients with focal impaired awareness seizures, NPE sleep recording demonstrated IEDs in 31 (25.6%) with no IEDs on the scalp electrodes although 33 patients (27.3%) had IEDs localized exclusively to the scalp electrodes.[26] In another study, twelve (16.6%) of 72 patients with focal impaired awareness seizures had IEDs. Five (6.9%) had paroxysmal discharges only in NPE with no diagnosable scalp discharges although four patients (5.6%) had IEDs on only scalp electrodes.[30] In a study that investigated IEDs with 10-20 system electrodes and NPE in 227 psychiatric patients, 26 (11.5%) patients showed IEDs. IEDs were visible only on NPE in 11 (42.3%) of the 26.[28] In a study which investigated the usefulness of ATE, NPE, and mini-sphenoidal electrodes in 50 patients with known or suspected focal impaired awareness seizures, of 20 patients with IEDs, 13.2% of the spikes were detected only by NPE and 1 patient had spikes seen only in this derivation irrespective of 4 patients unsatisfactory to NPE recording due to artifacts. In combination with ATE, NPE detected 97% of IEDs compared to 58% by the standard electrode placement in 20 patients.[27] On the other hand, other studies found no additive value for NPE compared to ear and temporal electrodes. No recording showed IEDs to be exclusively recorded by NPE in 302 EEGs of psychiatric patients who had a clinical suspicion of temporal lobe dysfunction or seizures, abnormal activity in the temporal area on routine EEGs, or special request by the referring physician.[46] In another study, 103 EEGs were performed on 98 patients suspected of having epilepsy who had a previous normal record.[25] IEDs were detected in 22% of the recordings. IEDs detected in NPE were invariably seen in ear and ATE derivations using carefully designed montages, and EEG diagnosis was not altered by use of NPE. Forty-four EEGs were performed on 44 patients with focal impaired awareness seizures, simultaneously recording from NPE, SPE, and ear electrodes.[14] Spikes were noted in SPE derivations in 25 records, in ear derivations in 23 records, and NPE derivations in 20 records. A total of 875 spikes were counted, SPE showing 99%, NPE 57%, and ear electrodes 54% of discharges, with greatest amplitudes generally seen in SPE derivations. In a study which examined the usefulness of multiple electrodes in 20 patients with seizures of suspected anterior temporal origin, ATE detected significantly more spikes than NPE (86.4% versus 62.9%) and virtually all (92-97%) NPE spikes were simultaneously detected by SPE, mandibular notch surface electrodes, mandibular notch subdermal electrodes, or ATE.[19]

There are several different points in methods of our study compared to previous studies. The purpose of our study was not to compare NPE with ATE and 10-20 system electrodes but to investigate additional value of NPE recording. Therefore, the proportion of patients with IEDs exclusively recorded on ATE or other electrodes was not investigated separately. Only patients with definite or suspected TLE were included to verify the usefulness of NPE. Patients with definite or suspected extra TLEs based on seizure semiology, EEG finding, and MRI finding, were excluded. Previous studies except for one study[31] used analogue EEGs which were displayed simultaneously with NPE, ATE, and other electrodes. Therefore, when IEDs are definitely detected on a specific electrode, interpreters could see EEG changes occurring on the other electrodes at the same time and then may easily recognize small amplitude of IEDs on electrodes for comparison. Furthermore, much experienced EEG specialists who conducted previous studies would detect IED proficiently. We analyzed separately NPE recordings with ATE and 10-20 system electrodes and ATE recordings with 10-20 system electrodes, which were obtainable after digital EEG acquisition. Also, conservative interpretation was warranted whenever doubt existed, which reflects low false positive rates in our study, although this interpretation could provide a bias to increased detection of IEDs in NPE recording.

Another purpose of our study was to show more usefulness of NPE when less EEG-experienced neurologists interpret EEGs. Less EEG-experienced physicians might not detect small amplitude of IEDs compared with more experienced physicians. Although the detection rates of IEDs in EEG interpretation with NPE were significantly superior to those in EEG interpretation with NPE in all three interpreters, the effect was stronger as having less experience for EEG interpretation. In our study, maximal amplitude of IEDs was more frequently found on NPE than on other electrodes, and the proportion of EEGs with IEDs $\geq$ 10 in NPE recording were higher than that of EEGs with IEDs ≥ 10 in non-NPE recording, which may reflect easier identification of IEDs in the interpretation of NPE recording by less EEG-experienced physicians. Also, the proportion of EEGs with IEDs < 10 in NPE recording were higher than that of EEGs with IEDs < 10 in non-NPE recording, which may suggest that NPE recording could be beneficial effect for the detection of IEDs compared with non-NPE recording that may show waveforms that were less sharp and less distinct from the background activity, that may not be regarded as IEDs. In this study, the agreements for IEDs in EEG interpretation increased to substantial degree between beginner and junior or senior (κ: 0.717 and κ: 0.678, respectively) and among three interpreters (κ: 0.703) with NPE recording from moderate degree between beginner and junior or senior (κ: 0.453 and κ: 0.479, respectively) and among three interpreters (κ: 0.536) with non-NPE, which are comparable to agreement rate (κ: 0.50 among four neurologists) for IEDs detection in previous study.[34]

In this study, another interesting finding was that bilateral IEDs were more frequently detected in NPE recording than in non-NPE. It has been widely known that bilateral independent temporal IEDs were found in about half of patients with TLE on long-term EEG monitoring.[47-49] The existence of bilateral IEDs in TLE may be commonly regarded as bitemporal excitability, implicating association with bilateral TLE and poor surgical outcome.[50-52] Our study suggests that the use of NPE on routine EEGs could detect more bilateral IEDs in patients with TLE in addition to higher sensitivity of IEDs, which may give clinical significance in the determination of epileptogenic focus.

EEG recording with NPE has been considered as having some problems, such as technical difficulty, patient’s discomfort, and vulnerability to movement artifacts leading to unsatisfactory EEG recording. However, contrary to these concerns, incomplete EEG cases based on the actual experience of NPE study were very scare (2.4%).[26] Despite of enrolled all patients who have psychiatric problem, additional NPE were performed without any trouble.[46] Although unsatisfactory EEG recording by NPE contamination was relative uncommon (7.7%), the amount of these unacceptable EEG has been found to decrease markedly as EEG technicians become more skilled at NPE.[29] Most of all, the use of NPE has never been reported to patients with serious complication.[31]

The simultaneous use of NPE and ATE had been performed for almost 30 years at Severance Hospital. NPE had been routinely used in the initial EEG recording for all patients who had clinically definite or suspected seizures and visited the outpatient epilepsy clinic, except for epilepsy patients with known or clinically definite generalized epilepsy, lack of cooperation such as mental retardation, young age, and psychiatric problems, or technical difficulty due to the nasal cavity problems. NPE were placed by trained technologists. In our experience, incomplete NPE recording due to technical and patient’s problems have been extremely rare.

Our study has some biases. The difference in the detection rates of IEDs between beginner and junior decreased from 22.8% in non-NPE recording to 8.7% in NPE recording and between beginner and senior, 24.9% to 13.9%. Too conservative interpretation in non-NPE recording could overestimate the detection rates in IEDs in NPE recording, particularly apparently in EEG beginner. These findings may indicate inadequacy of EEG interpretation by EEG beginner because the detection rates of IEDs in NPE recording were still lower compared with those of EEG specialists, also as seen in much lower proportion of IEDs ≥ 10 even in EEGs with IEDs in EEG interpretation with NPE and non-NPE by beginner. Also, it cannot be excluded that a greater influence by senior EEG specialist was exerted during consensus meetings to draw final results, which could be distorted true results. However, considering small differences in the detection rates of IEDs between two EEG specialists in both NPE and non-NPE recordings, such possibility seems to be low.

V CONCLUSION

This study suggests that NPE recording may be useful to detect IEDs and determine the laterality of IEDs than non-NPE recording. This beneficial effect of NPE recording may exist regardless of the experience degree of EEG interpretation although greater for EEG beginner. In addition, the agreement for the detection of IEDs among EEG interpreters may significantly improve in the interpretation of NPE recording than that in non-NPE recording. This study suggests that NPE recording may be recommended in routine EEGs for evaluation of patients with epilepsy, particularly TLE.

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ABSTRACT(IN KOREAN)

측두엽 뇌전증에서 비인두 전극의 유용성

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배경: 10-20 전극 체계 전극으로만 시행한 뇌파로 뇌전증모양파 확인이 어려운 측두엽 뇌전증의 비율은 적지 않다. 이러한 측두엽 뇌전증에 대한 정확한 뇌파 검사를 위하여 추가적으로 사용되는 전극 중에 하나인 비인두 전극은 선행 연구에서 그 임상적인 의미와 뇌파 판독의 유용성은 아직까지 논란이 있는 상황이다.
연구목적: 전측 측두엽 전극과 비인두 전극을 이용하여 측두엽 뇌전증의 뇌파 판독을 할 때 뇌전증모양파의 발견율과 병소의 위치를 확인하는데 어떠한 영향을 미치는지 확인하고자 하였다. 또한, 측두엽 뇌전증의 아형에 따라 각각의 추가 전극의 특장점을 확인하고자 하였다.
방법: 측두엽 뇌전증 환자들 중에서 비인두 전극과 전측 측두엽 전극이 동시에 사용된 229명 환자들의 뇌파를 후향적으로 분석하였다. 뇌파는 두개의 군으로 구분하여 10-20 전극 체계에 전측 측두엽 전극만을 사용하여 판독한 군과 전측 측두엽 전극과 비인두 전극을 모두 사용한 군으로 구분하였다. 판독은 2명의 뇌파 전문가와 1명의 뇌파 입문자가 독립적으로 판독하였다. 이후 판독에 대한 불일치를 보이는 것이나 애매한 소견에 대한 의견합의 절차를 거쳤다.
결과: 뇌파 입문자와 2명의 전문가에 대한 비인두 전극/전측 측두엽 전극에 대한 뇌전증모양파의 발견율은 각기 순서대로 60.3%/27.1%, 69.0%/49.8%, 74.2%/52.0% 비인두 전극을 적용한 군이 뇌파의 경험과 관계없이 높게 확인되었다 ($p < 0.001$). 비인두 전극을 이용한 군이 판독자간의 판독 일치율도 의미 있게 상승하였다(κappa 0.703 versus 0.536). 또한, 비인두 전극의 사용은 내측두엽과 비병소 측두엽에서 유의미하게 뇌전증 모양파가 확인되었다.($p < 0.001$).
결론: 비인두 전극을 이용한 뇌파 판독은 뇌전증모양파의 발견에 의

미있게 도움을 준다. 특히, 내측두엽과 비병소 측두엽의 뇌파를 판독하는 경우에 비인두 전극의 적용 효과가 확실하게 확인되었다.

핵심되는 말: 비인두 전극, 전측 측두엽 전극, 10-20 전극 체계,측두엽 뇌전증