Practical Dose Parameter Values for the Prediction of the Adverse Effect of Neurointerventional Radiation: Relationship Between the Dose Parameters and Temporary Alopecia After Intracranial Coil Embolization

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■ OBJECTIVE: **To present values for the dose parameters predictive of alopecia as an adverse effect induced by neuroembolization using a biplane fluoroscopy.**

■ METHODS: **This study included a total of 151 patients (52 men, mean age of 55.1 ± 12.2 years) treated for intracranial neuroembolization between 2014 to 2018 with the following criteria: 1) obtainable dose report with digital subtraction angiographic image records, 2) no history of radiation exposure 6 months prior to the first procedure, and 3) and clinical follow-up performed through 12 months following the procedure. Patients were divided into 2 groups according to their presentation of alopecia during the follow-up period.**

■ RESULTS: **Eighteen (11.9%) patients developed alopecia 10 to 30 days after the procedure (average: 18.5 ± 5.3 days). Sixteen (88.9%) patients in the alopecia group were affected by projection of the A-plane fluoroscopy. Area under the receiver operating characteristic analysis curves of 0.865 ($P = 0.000$) and 0.831 ($P = 0.000$) were used to compute the optimal A-plane dose area product (255.4 Gy-cm^2; sensitivity: 0.875; specificity: 0.805; Youden $J = 0.682$) and cumulative dose (4437.5 mGy; sensitivity, 0.750; specificity, 0.805; Youden $J = 0.556$) cutoff values, respectively, capable of distinguishing patients with alopecia (n = 16) from subtotal patients (n = 149).**

■ CONCLUSIONS: **The dose area product and the cumulative dose may be useful, intuitive factors for predicting the adverse effects of the neurointerventional radiation. Further multicenter research should be performed to confirm the efficacy and utility of the reference values of dose area product and cumulative dose for preventing excessive irradiation during neurointerventional procedures.**

INTRODUCTION

Neurointerventional radiologic procedures have been extensively developed by the evolution of fluoroscopic machines, especially that of biplane angiographic units[1]; the development of the biplane machine can improve the accuracy and the time of the procedure because it allows the use of diverse angles as well as the subsequent 3-dimensional reconstruction of images in cases of cerebrovascular lesions; nevertheless, the biplane machine elevates the risk of exposure to high doses of radiation that threatens both patients and physicians.[2-4] Radiation-related scalp injuries vary from erythema to desquamation, temporary/permanent alopecia, and—in rare cases—tumor.[1,3,5-8] The most typical and prominent sign among the aforementioned injuries is likely temporary alopecia, as erythema and desquamation may be concealed by scalp hair and undetected even though the scalp itself may evince such symptoms.[1] The boundaries of rectangular-shaped incidences of alopecia presenting after neuroembolization under the biplane fluoroscopy and localized at 1 side of 2 projections may resemble fields of view (Figure 1). It has been suggested that locally administered

Key words
- Alopecia
- Dose
- Embolization
- Fluoroscopy
- Radiation

Abbreviations and Acronyms
AUC: Area under the receiver operating characteristic analysis curves
CD: Cumulative dose
DAP: Dose area product
ESD: Entrance skin dose
ICRP: International Commission on Radiological Protection
ROC: Receiver operating characteristic
TLD: Thermoluminescence dosemeter

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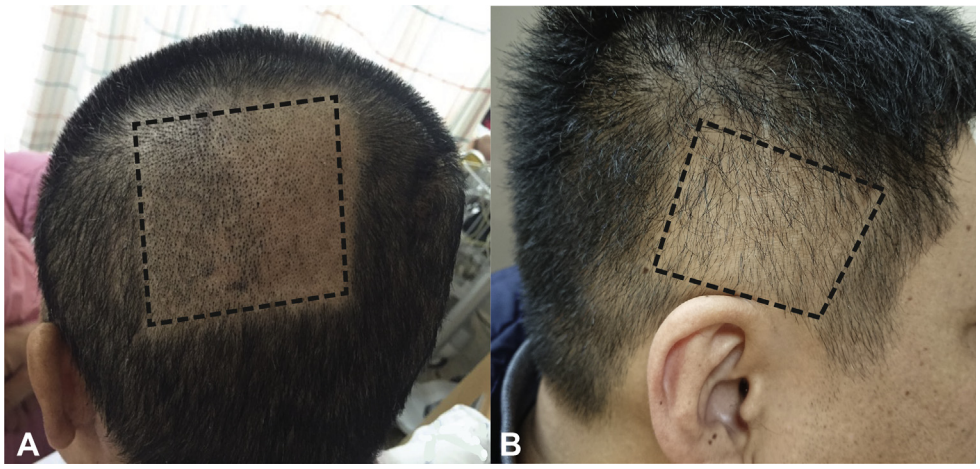

Figure 1. Photos show alopecia developed after intracranial coil embolization. Rectangular alopecia pattern resembles the field of view. The alopecia regions (*within dashed line*, **A** and **B**) fell within the trajectories of the irradiating projections of the A-plane and B-plane fluoroscopic arms of the angiographic machine, respectively.

radiation may adversely affect a faced region despite scattering projection; multiple studies have attempted to document the extent of fluoroscopy-induced exposure of the patient to radiation, but these previous investigations have only executed limited calculations of the radiation dose of the monoplane machine or the sum of the total radiation dose attributable to the biplane machine.[1-7,9-13] Moreover, the entrance skin dose (ESD, 3–7 Gy for temporary alopecia) documented by the International Commission on Radiological Protection (ICRP)[8] is unlikely to be clinically available during the performance of procedures unless a thermoluminescence dosemeter (TLD) is used; however, the values of the TLD should be checked even after the procedure and other dose mapping methods using TLD arrays or dosimetric film are rarely used because of their inconvenience and cost.[14] Alternatively, a dose area product (DAP) and a cumulative dose (CD) meter displayed by angiography systems and presented in patient dose reports are commonly used to estimate the radiation dose. When the DAP and CD meter are used in tandem, they provide the best estimate of the ESD currently available.[2,15] Moreover, most practitioners may record DAP, CD, fluoroscopic time (minutes), and the number of frames in real time as patient dose indicators because monitoring these factors in real time and attempts to reduce them while maintaining image quality and patient safety is essential to the successful outcome of each case.[16] Unfortunately, however, some practitioners may pay more attention and give more weight to image quality and the final result of the procedure than to the radiation dose administered during the procedure because the typical symptoms consequent of high-dose radiation may commonly present several days after the procedure.

The purpose of this retrospective study was to compare the DAP, CD, and other parameters in patients with and without radiation-induced alopecia after neuroembolization was performed using a biplane angiographic unit and to identify values of the dose parameters predictive of adverse effects resultant of the procedure.

METHODS

Study Population

We enrolled patients who were treated for cerebrovascular lesions using coil embolization in a single institute between 2014 and 2018. Of the 475 patients initially identified, 151 patients were retrospectively analyzed on account of having satisfied the following criteria: 1) underwent endovascular treatment for intracranial aneurysm, 2) procedure performed using a biplane angiography unit, 3) obtainable dose report after digital subtraction angiography, 4) no history of radiation exposure within the 6 months prior to the first procedure, 5) clinical follow-up through over 12 months after the procedure. According to the presentation of alopecia during the follow-up period, the patients were divided 2 groups: non-alopecia and alopecia. The study groups consisted of 52 men and 99 women with a mean age of 55.1 ± 12.2 years. The demographics of the 2 groups are presented in **Table 1**. The 2 groups did not differ significantly in sex, age, lesion distributions, or methods of coil embolization (**Table 1**).

Procedures, Angiographic System, and Parameters

The patient dose indicators fluoroscopic time (in minutes), number of frames, DAP (in Gy-cm^2), and CD (in mGy) were recorded in each procedure report. All procedures were performed by 2 experienced neurointerventionalists using a biplane angiographic unit (Axiom Artis zee, Siemens Healthcare, Erlangen, Germany) with a flat panel detector: A and B planes featured a variable field of view 48-42-32-22-16-11 cm. The total filtration was 0.3 (mmCu). The obtainment of frames was set to 4 frames/second

Table 1. Demographics of the 151 Patients Who Underwent Intracranial Coil Embolization

	Total	Non-alopecia Group	Alopecia Group	
	N = 151	n = 133 (88.1%)	n = 18 (11.9%)	*P* Value
Sex (female, %)	99 (65.6)	87 (65.4)	12 (66.7)	0.916
Age in years, mean ± SD	55.1 ± 12.2	55.3 ± 12.3	53.8 ± 11.0	0.643
Location of lesion (%)				0.127
ICA	62 (41.1)	58 (43.6)	4 (22.2)	
ACA	47 (31.1)	38 (28.6)	9 (50.0)	
MCA	21 (13.9)	18 (13.5)	3 (16.7)	
VA	10 (6.6)	9 (6.8)	1 (5.6)	
BA	9 (6.0)	9 (6.8)	0 (0)	
Others	2 (1.3)	1 (0.8)	1 (5.6)	
Methods of coil embolization (%)				0.155
Single catheter	90 (59.6)	82 (61.7)	8 (44.4)	
Double catheter	17 (11.3)	12 (9.0)	5 (27.8)	
Stent-assisted	33 (21.9)	28 (21.1)	5 (27.8)	
Only stenting	6 (4.0)	6 (4.5)	0 (0)	
Balloon-assisted	5 (3.3)	5 (3.8)	0 (0)	
Rotational angiography				
Number (IQR)	2 (2–2)	2 (2–2)	2 (2–3.3)	0.072
DAP (μGy-m^2)	985.7 ± 190.3	990.1 ± 172.4	953.3 ± 295.9	0.443
CD (mGy)	35.6 ± 6.7	35.7 ± 6.1	35.0 ± 10.5	0.657
Frames	132.7 ± 24.3	133.7 ± 23.2	125.2 ± 31.3	0.167
Total				
Procedure time (minutes)	110.4 ± 46.7	105.1 ± 42.2	149.9 ± 59.4	0.006*
Fluoroscopic time (minutes)	79.5 ± 41.0	76.6 ± 39.5	100.6 ± 47.3	0.019*
Exposure (n, IQR)	33 (26–42)	32 (25–39)	45 (32.8–49.3)	0.000*
DAP (μGy-m^2)	31490.0 ± 13855.9	29419.0 ± 12702.2	46792.9 ± 12636.6	0.000*
CD (mGy)	5954.1 ± 3160.0	5499.2 ± 2648.0	9316.0 ± 4480.7	0.002*
A-plane				
Voltage (kV)	88.7 ± 9.1	88.5 ± 8.3	90.4 ± 13.8	0.569
Current (mA)	322.8 ± 185.7	310.3 ± 173.1	415.9 ± 247.2	0.095
FOV (cm)	14.6 ± 4.7	14.2 ± 4.3	16.8 ± 6.8	0.132
Frames (n)	179.3 ± 92.8	170.6 ± 87.7	244.4 ± 106.2	0.001*
Fluoroscopic time (minute)	43.0 ± 21.6	41.1 ± 20.6	56.8 ± 24.2	0.003*
DAP (μGy-m^2)	20854.0 ± 9861.2	19306.3 ± 9049.1	32290.2 ± 8061.9	0.000*
CD (mGy)	3797.9 ± 2112.2	3462.6 ± 1560.7	6275.5 ± 3615.9	0.000*
B-plane				
Voltage (kV)	80.2 ± 6.8	80.3 ± 7.0	79.8 ± 5.8	0.803
Current (mA)	286.9 ± 111.5	276.0 ± 86.5	367.3 ± 209.6	0.084
FOV (cm)	19.0 ± 6.5	19.1 ± 17.9	6.6 ± 5.2	0.477

Continues

Table 1. Continued

	Total	Non-alopecia Group	Alopecia Group	
	N = 151	n = 133 (88.1%)	n = 18 (11.9%)	*P* Value
Frames (n)	179.3 ± 92.8	170.5 ± 87.7	244.4 ± 106.2	0.001*
Fluoroscopic time (minute)	36.5 ± 20.4	35.5 ± 19.4	43.9 ± 26.4	0.104
DAP (μGy-m^2)	10636.0 ± 6108.3	10112.7 ± 5807.8	14502.7 ± 7024.3	0.004*
CD (mGy)	2156.3 ± 1364.7	2036.6 ± 1316.9	3040.5 ± 1423.8	0.003*

ACA, anterior cerebral artery; BA, basilar artery; CD, cumulative dose; DAP, dose area product; FOV, field of view; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; VA, vertebral artery.
*$P < 0.05$.

for plane angiography and 30 frames/second for rotational angiography. The angiographic system included a DAP and CD meter. The parameters obtained from the dose reports were compared between the 2 groups for each plane and for total dose (Table 1). Procedure time was calculated with the following equation: last scene time−first scene time. Fluoroscopic time was obtained from the dose report. The DAP (μGy-m^2) was divided by 100 and converted to DAP (Gy-cm^2) to allow for comparisons with other values in the literature.

Statistical Analysis

Continuous data that were normally distributed according to the Kolmogorov-Smirnov test were analyzed using Student's t test. The χ^2 and Fisher's exact tests were used for the comparison of categorical data between the two groups. Receiver operating characteristic (ROC) analyses were performed, and the area under the ROC analysis curves (AUC) were used to evaluate the diagnostic performance of the measured the dose parameters as well as to differentiate patients with/without alopecia. The Youden J index was used to identify the optimal cutoff values for the differentiation of patients.[17] P-values of <0.05 (2-tailed) were considered significant. Statistical analyses were performed using SPSS version 23 (IBM, Armonk, NY).

RESULTS

Eighteen (11.9%) patients developed alopecia at 10 to 30 days after the procedure (average: 18.5 ± 5.3 days) and spontaneously improved within 1 to 4 months after developing alopecia (average: 2.8 ± 0.8 months). The locations of the lesions and methods of coil embolization were not significantly different between the 2 groups. Rotational angiography performed to yield the 3-dimensional reconstruction was similarly performed within both groups. Sixteen (88.9%) members of the alopecia group were affected by the projection of the A-plane fluoroscopy.

Analysis of Dose Report

The overall comparison revealed that the procedure and fluoroscopic time were significantly longer in the alopecia group than in the non-alopecia group (P = 0.006 and P = 0.019, respectively). The number of exposures in the alopecia group was also significantly greater than in the non-alopecia group (P = 0.000). DAP and CD among patients who developed alopecia were significantly higher than those without alopecia (P = 0.000 and P = 0.002, respectively).

Comparison of the A-plane alone demonstrated that the number of frames in the alopecia group was significantly more than that of the non-alopecia group (P = 0.001). The fluoroscopic time in the alopecia group was significantly longer than in the non-alopecia group (P = 0.003). The DAP and CD of alopecia group were significantly higher than those of the non-alopecia group (P = 0.000 and P = 0.000, respectively).

Comparison of the B-plane alone indicated that the number of frames in the alopecia group was significantly more than that of the non-alopecia group (P = 0.001), whereas there was no significant difference in fluoroscopic time between the two groups. DAP and CD of the alopecia group were significantly higher than those of the non-alopecia group (P = 0.004 and P = 0.003, respectively).

Correlation Analysis of the Fluoroscopic Time, Number of Frames, DAP, and CD

The fluoroscopic time was significantly correlated with both the DAP (Pearson r = 0.699, P = 0.000, Figure 2A) and CD (Pearson r = 0.811, P = 0.000, Figure 2B). A significant correlation was also observed between the number of frames and both DAP (Pearson r = 0.532, P = 0.000, Figure 2C) and CD (Pearson r = 0.648, P = 0.000, Figure 2D).

Analysis of ROC Curve

AUCs of 0.864 (P = 0.000) and 0.818 (P = 0.000) were used to compute optimal DAP (317.2 Gy-cm^2; sensitivity: 0.944; specificity: 0.662; Youden J = 0.604) and CD (6583.5 mGy; sensitivity: 0.833; specificity: 0.744; Youden J = 0.578) cutoff values, respectively, capable of distinguishing patients with alopecia (n = 18) from total patients (n = 151) (Figure 3A).

In a similar fashion, AUCs of 0.865 (P = 0.000) and 0.831 (P = 0.000) were used to compute the optimal A-plane DAP (255.4 Gy-cm^2; sensitivity: 0.875; specificity: 0.805; Youden J = 0.682)

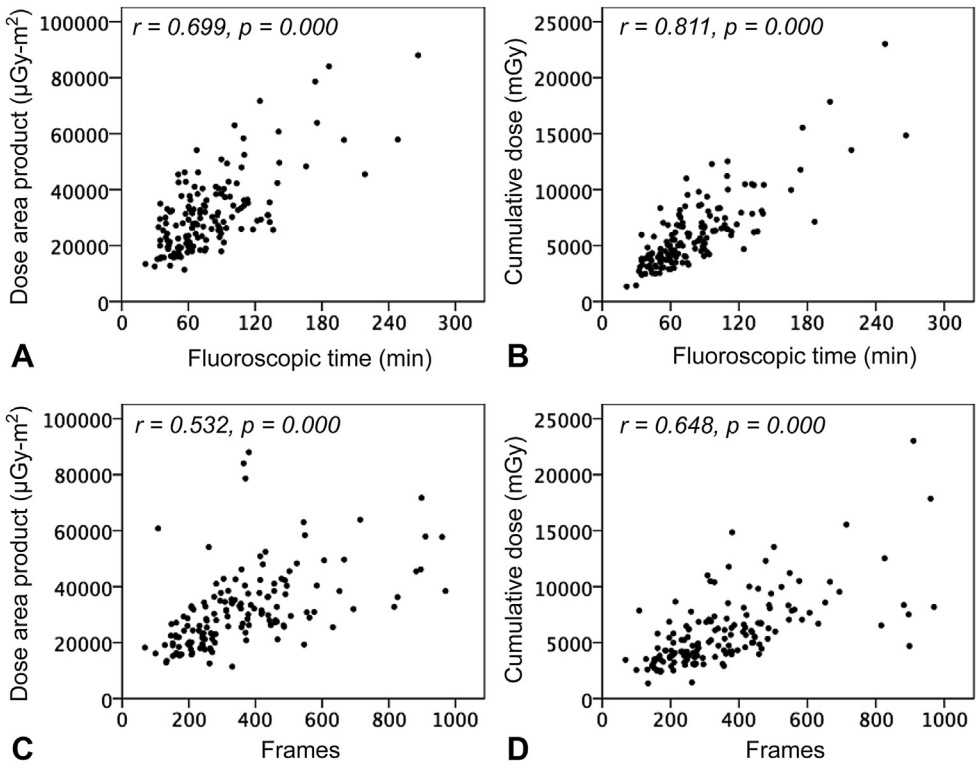

Figure 2. Scatter plots for the correlation analyses of fluoroscopic time with dose area product and cumulative dose (**A** and **B**), and the number of frames with the dose area product and the cumulative dose (**C** and **D**).

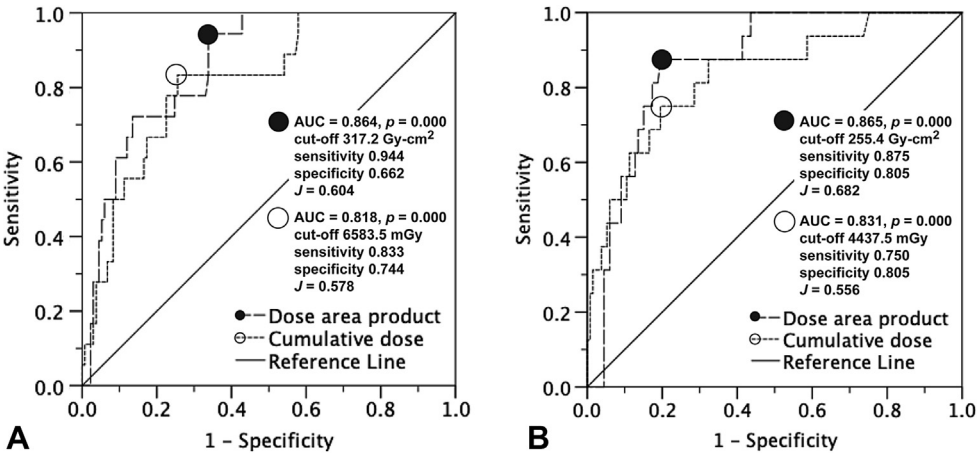

Figure 3. The receiver operating characteristic curves for the dose area product and cumulative dose with a cutoff value (at black and white circles) and Youden index (*J*) to predict radiation-induced alopecia. (**A**) Area under curve (AUC) comparison between the dose area product and the cumulative dose for alopecia in the total population. (**B**) AUC comparison between the dose area product and the cumulative dose for alopecia in patients affected by A-plane fluoroscopy.

Table 2. Result Comparison: This Study and Others

References	No. of Total Patients	No. of Alopecia (%)	DAP (Gy-cm^2)	CD (Gy)	ESD (Gy)	Year
This study	151	18 (11.9)	292.7–717.1	4.3–23.0		
Magrassi et al.	107	22 (21)	350.0–1694.7		1.2–5.4	2012
Neil et al.	11	3 (27)	235.8–463.4		2.9–5.7	2010
Suzuki et al.	79	6 (8)	533.3–1500.0		2.7–5.6	2008
ICRP	NA	NA	>1100*		3.0–7.0	2000
Norbash et al.	87	9 (10)	NA†			1996

CD, cumulative dose; DAP, dose area product; ESD, entrance skin dose; ICRP, International Commission on Radiological Protection; NA: not applicable.
*Derived from a value calculated by D'Ercol et al. using patients with temporary epilation after interventional radiation.
†Did not provided an interpolation construct between skin entrance dose and DAP.

and CD (4437.5 mGy; sensitivity: 0.750; specificity: 0.805; Youden $J = 0.556$) cutoff values, respectively, capable of distinguishing patients with alopecia (n = 16) from subtotal patients (n = 149) (Figure 3B).

DISCUSSION

We observed that the procedure and the fluoroscopic time of the alopecia group were longer than those of the non-alopecia group and that the DAP and CD of the alopecia group were higher than those of the non-alopecia group.

Projection of the A-plane resulted in significantly more alopecia patients than did projection of the B-plane; the length of time, DAP, and CD of patients with alopecia affected by A-plane fluoroscopy were significantly more than those of the non-alopecia group. We found the DAP and the CD to range from 292.7 to 717.1 Gy-cm^2 and 4.3 to 23.0 Gy, respectively; these ranges correspond well with those associated with adverse radiation-induced skin injury of reported earlier investigations.[1,3,7,10] The presently observed rate of the radiation-induced alopecia (11.9%) falls within the range reported in prior studies (5% to 27%).[1,3,7,10,18,19] According to a recommendation provided by the ICRP, all patients exposed to radiation that equals or exceeds 3 Gy require follow-up at 10 to 14 days after the procedure in case they present temporary alopecia[8]; our mean presentation period (18.5 days) supports the necessity to monitor at-risk-suspecting patients. The average period (2.8 months) of improvement also agreed with previously reported data (2 to 4 months after irradiation).[5]

Suzuki et al.[10] reported that although the ESDs were estimated by using radiosensitive indicators and that DAPs were derived from a linear regression formula with DAP and ESD as inputs (maximum ESD [Gy] = 1.100 + 0.003 x DAP [Gy-cm^2]), temporary alopecia was detected in a DAP range of 533.3 to 1500.0 Gy-cm^2. Studying the relationship among the ESD, the CD, and the DAP, Neil et al.[3] documented 3 patients with hair loss, accounting for 27% of 11 patients, with the following DAPs: 235.8, 260.2, and 463.4 Gy-cm^2 (calculated by using a mean ratio of CD to DAP [0.0123]). Magrassi et al.[1] revealed that 22 patients with alopecia, accounting for 21% of 22 patients, had DAPs of 350.0 to 1694.7 Gy-cm^2, which were derived from a maximum ESD with a constant factor (0.0032 cm^2). Most of the investigators obtained ESD by using dosimeters like TLD; otherwise, the ESD was calculated and derived from the DAP by using conversion factors. In a similar fashion, although the ICRP[8] documented the threshold of the acute radiation dose causative of temporary alopecia to be between 3 and 7 Gy, the threshold could be converted to DAP (1034.5 Gy-cm^2) by using a constructive interpolation line and conversion factor (0.0029).[9] Our result fell within or below the ranges reported by prior studies (Table 2).

The DAP and the CD may be more applicable than the ESD in terms of practical convenience and effectiveness for real-time radiation dose estimation.[2,20,21] The CD is the absorbed dose accumulated at a specific point in space relative to the fluoroscopic gantry (the interventional reference point) during a procedure.[3,14] Therefore, the CD should allow the practitioners to yield the dose delivered to the patient's skin and provide a better indication of deterministic effects, whereas the DAP can be used to estimate the effective dose and as a risk indicator for stochastic effects.[4,22-24] The CD is likely to overestimate the ESD, however, if the x-ray tube will irradiate the patient from different angles.[3] Some investigators have suggested that the DAP is not suitable for monitoring because of the diversity of the projections during the procedure and the weak correlation between the DAP and the ESD measured directly on the patient.[9,23,25,26] Nevertheless, some researchers have documented reasonable correlations between the CD and the ESD.[3,10,22,27,28] In addition, the constant conversion factors constructed in prior studies investigating both interventional cardiology[22,24,26,29] and interventional neuroradiology[1,3,6,9,10] could be used to establish the ESD from the DAP and the CD in the absence of a direct measurement.[25] Moreover, the projection angles of 2 x-ray tubes in a neuroradiologic procedure may be consistent during the procedure time after the working angles are confirmed in most of neurointerventional cases. In this study, we found that the DAP and the CD yielded significantly greater AUCs than did the other parameters only by a narrow margin. Therefore, both the DAP and the CD may be valuable indicators acceptable for real-time monitoring and predicting the adverse effect of radiation in the interventional neuroradiologic procedures.

Fluoroscopic time alone correlates poorly with the ESD and underestimates the risk of radiation-induced skin effects.[15,28] The

fluoroscopic time and the number of frames can, when used in tandem, provide a better guide concerning patient dose but are not indicators of dose in and of themselves.[14] However, if any of the aforementioned parameters are unavailable, fluoroscopic time and the number of frames can be used for recording patient radiation dose without the input of the patient's height and weight until other means become available because the head is associated with greater consistency than any other part of the body.[14] Indeed, the present study showed a significantly positive correlation among the fluoroscopic time, the number of frames, the DAP, and the CD. Consequently, an effort of reducing the fluoroscopic time and number of frames can influence reducing the DAP and CD because a modification of the fluoroscopic time and number of frames might be likely to be handled by the practitioners.

Prior investigators have suggested that a dose spreading technique achieved by periodically rotating the fluoroscopes helps to diminish the radiation dose at any particular area.[9,30] The present study, however, changed the angle of the x-ray tube during the procedures administered to a total 11 (7.3%) patients composed of 7 (5.3%) in the non-alopecia group and 4 (22.2%) in the alopecia group despite the small population. We deduced that the fluoroscopic time, number of frames, DAP, and CD contributed more to a particular area of the alopecia than did dose spreading, although the alopecia group was associated with more changes in the fluoroscopic tube angle than was the non-alopecia group.

In a prior study of further modifying other parameters, Pearl et al.[31] demonstrated that variable frame rates and lower pulse rate reduced the DAP and CD during fluoroscopy. Yi et al.[32] proposed that the DAP and CD were reduced by changing the amount of radiation emitted per unit without modifying the frame rate or pulse rate during fluoroscopy. Therefore, the radiation dose may be further reduced by not only the fluoroscopic time and number of frames but also other parameters setting including the frame rate, pulse rate and amount of radiation emitted per unit.

Limitations

First, this is a retrospective study. Second, an uncertainty of up to 40% has been associated with the measurement of DAP due to deviations from the nominal values of the ESD.[9,14,20] However, various studies have demonstrated that for a specific system, procedure, and protocol, there is often a reasonable correlation between the DAP and the ESD, and this enables identification of a warning threshold for the DAP; above this level, it is likely that the ESD could cause skin damage.[9] In addition, the DAP could distribute more reliably when paired with the CD than when used alone. Third, in this study, most of the fluoroscopic tubes that caused the alopecia featured an A-plane geometry. Only 2 (11.1%) cases were induced by B-plane fluoroscopic tubes; although the exact causes of these incidences are unclear, these cases showed no significant differences from cases of alopecia induced by A-plane fluoroscopic tube. We deduce that the exceptional cases could result from the unavoidable overlapping of areas of radiation projection with the uncertainty under the sensitivity for a given area of skin. Fourth, the diagnostic reference level, which is composed of the DAP, the number of exposures, and the fluoroscopic time, can yield information regarding acceptable radiation doses.[2,12,13,25] However, the diagnostic reference level may be just a distributional value because it is derived from the 75th percentile of the distribution—regardless of any adverse skin effect. The reference value, when used as the cutoff value for the DAP and the CD according to definite adverse skin effect, could be enough to compensate for the diagnostic reference level.

CONCLUSIONS

The DAP and the CD may be useful, intuitive factors predictive of the adverse effect of neurointerventional radiation. Further multicenter studies are required to confirm the efficacy and utility of DAP and CD reference values that may inform the prevention of excessive irradiation during neurointerventional procedures.

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Compliance with ethical standards: This retrospective study was approved by the local institutional review board (No. GCIRB2019-084). All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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