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Original Article

Evaluation of the value of indocyanine green fluorescein angiography in the intraoperative clipping effect of intracranial aneurysms

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Abstract: Objective: To evaluate indocyanine green fluorescein angiography (ICGA) in the protection of perforating vessel during intracranial aneurysm clipping. Methods: A total of 52 patients who underwent intracranial aneurysm clipping surgery from January 2013 to March 2017 in Neurosurgery Department of The Second Affiliated Hospital of Zhejiang University School of Medicine were selected. The patients were divided into two groups according to the grouping standard of whether use the ICGA monitoring. The observation group (26 cases) was using ICGA during intracranial aneurysm clipping surgery from February 2015 to March 2017. In the control group (26 cases), the same number of cases who underwent intracranial aneurysm clipping were selected in order from January 2013 to January 2015, and ICGA was not performed during the surgery. The number of ICGA examinations and the adjustment of aneurysm clips were recorded. The reoperation rate, hospitalization time, postoperative Glasgow coma scale (GOS) scores, and the occurrence of postoperative non-intracranial complications (pulmonary, urinary tract infection, gastrointestinal bleeding, non-cerebral salt consumption, and electrolyte disorders caused by dissonance of antidiuretic hormone secretion) were compared between the two groups of patients. Results: ICGA was performed 30 times in 26 cases of aneurysm clipping in the observation group, of which 23 cases after aneurysm clipping were confirmed by ICGA that the aneurysm was completely clipped. The parent artery was unobstructed and no stenosis was found. There was residual aneurysm in 1 case of anterior communicating artery aneurysm and 1 case of posterior communicating artery aneurysm, and 1 case of posterior communicating artery stenosis. During the surgery, the position of the aneurysm clip was changed or additional aneurysm clip was added. After that, ICGA was performed again and it was found that the perforating branch had good development and no stenosis of the parent artery. After surgery, all enrolled subjects were reviewed by digital subtraction angiography, and there was no case of ischemic cerebral infarction. The postoperative hospitalization time, reoperation rate, and postoperative GOS score of the two groups were compared, and the observation group was significantly superior to those of the control group. The difference was statistically significant (all $P<0.05$). The incidence of complications in the observation group was significantly lower than that in the control group (7.70% vs. 15.40%), and the difference was statistically significant ($P<0.05$). Conclusion: ICGA can realize intraoperative real-time visual evaluation of aneurysm clipping and open condition of the parent artery and perforating artery, and can help to reasonably adjust the clipping plan and improve prognosis.

Keywords: Indocyanine green fluorescein angiography, aneurysm, microsurgery, prognosis

Introduction

In recent decades, rapid development of microsurgery equipment and devices has led to intracranial aneurysm clipping surgery becoming safer. However, Xue et al. reported that there was still 4.12%-12.23% of the parent artery, branch, or perforating artery occlusion after surgery, which seriously affected the postoperative rehabilitation effect [1]. Therefore, how to evaluate the clipping effect of the aneurysm in real time during the surgery is the most important concern of the surgeons [2]. Intraoperative digital subtraction angiography (DSA) is currently the "gold standard" for evaluating the effectiveness of aneurysm clipping, but it requires

complex equipment, radiation protection, and special training for operating personnel, so it is difficult to meet the requirements of intraoperative monitoring [3].

The indocyanine green fluorescein angiography (ICGA) technique is simple to operate, convenient, repeatable, and non-radioactive. It can assess in real-time and accurately determine the blood flow conditions of an aneurysm, and thus this technique has gradually received attention of most scholars in recent years [4]. In this research study, 26 cases of diagnosed aneurysm patients admitted to Neurosurgery Department of the Second Affiliated Hospital of Zhejiang University School of Medicine from February 2015 to March 2017 were selected as subjects. The clipping effect of aneurysm was evaluated by ICGA during intracranial aneurysm clipping, and was compared the surgical effect with 26 cases of aneurysm patients from January 2013 to January 2015 who did not undergo ICGA. The application value of ICGA in protection of perforating vessels during the surgery of aneurysm was evaluated.

Materials and methods

General information

A total of 52 patients who underwent intracranial aneurysm clipping surgery from January 2013 to March 2017 in the Neurosurgery Department of the Second Affiliated Hospital of Zhejiang University School of Medicine were selected. The patients were divided into two groups according to the grouping standard of whether use the ICGA monitoring. The observation group (26 cases) used ICGA during intracranial aneurysm clipping surgery from February 2015 to March 2017. In the control group (26 cases), the same number of cases that underwent intracranial aneurysm clipping was selected in order from January 2013 to January 2015, and ICGA was not performed during the surgery.

Inclusion criteria: DSA examination confirmed the diagnosis of aneurysm; Hunt-Hess grade was between I-IV; aged 25-75 years old; non-allergic constitution; no allergic history of iodine and dyes or imaging agent used for examination [5].

Exclusion criteria: Those with severe diabetes, cardiovascular diseases and respiratory diseases; those with severe vasospasm revealed by vascular examination; liver dysfunction; pregnancy and lactation [6].

The Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine approved this research, and both patients and their families expressed their knowledge of the advantages and disadvantages of the surgery and signed the informed consent.

Methods

Perioperative nursing and anesthesia methods were consistent in both groups of patients [7] and the surgeons were all senior doctors with lots of experience.

The observation group was approached from the vascular flank point of anterior cerebral artery. The peripheral blood vessels were gently separated under a medical microscope after the epidural space was quickly cut open. At the same time, the lateral fissure cistern, optic chiasm cistern, and carotid cistern were non-invasively separated and cerebrospinal fluid was discharged. Intracranial pressure in the brain tissue was evaluated. If the intracranial hypertension was elevated, the end plate was opened to further discharge the cerebrospinal fluid. The hemorrhage in operative field was flushed to obtain a clear and identifiable anatomical structure of the anterior cerebral communicating artery. According to the position of the anterior communicating artery, the direction of blood flow and other indications, the location of the anterior communicating artery aneurysm was found. The appropriate brain pressure plate was selected and the neck was fully exposed to the intracerebral aneurysm in the microscope field. The anatomical relationship between the aneurysm and the parent artery was clearly identified, and the blood flow direction of the peripheral direct current vascular was examined. At last the appropriate aneurysm clip release position was selected to clip the responsible aneurysm neck [8]. ICGA was performed to the area where the aneurysm neck clip was released. After dissolving 25 mg of indocyanine green in 15 mL of sterile water, 5 mL was quickly injected into the external jugular vein. About 3 to 5 seconds later, the image of angiogram appeared on the microscope display, and the contrast agent was repeatedly injected during

Table 1. Comparison of general data between two groups

Group	Observation group (n=26)	Control group (n=26)	Test value	P
Gender ratio (male/female)	14/12	13/13	0.023#	>0.05
Age (years)	43.63±9.11	42.79±8.56	0.011*	>0.05
Hunt-Hess Grade			0.033&	>0.05
I-II	22	21		
III-IV	4	5		
Aneurysm location			0.112&	>0.05
Anterior circulation	9	10		
Posterior communicating artery	9	8		
Middle cerebral artery	4	3		
Clinoid process and the lower segment	2	3		
Posterior circulation	2	2		
Aneurysm diameter			0.008&	>0.05
<1.5	23	22		
1.5-2.5	2	2		
>2.5	1	2		

Note: #Used chi square test; *used t test; &used non-parametric test.

the intraoperative interval. If the clipping did not reach expectations, ICGA was performed again to guide the adjustment of the position of aneurysm clip and re-imaging until the clip achieved satisfactory. All patients in the control group were also applied temporary blocking clips to block the supply artery and routinely clip the aneurysms according to the needs of the surgery.

DSA follow-up examination was performed to determine the presence of ischemic infarction in both groups [9].

Observation index

The hospitalization time, reoperation rate (reoperation rate = numbers of reoperation patients/total number of patients * 100%), postoperative Glasgow coma scale (GOS) score, and the incidence rate of postoperative non-intracranial complications (pulmonary infection, urinary tract infection, gastrointestinal bleeding, non-cerebral salt consumption and electrolyte disorders caused by dissonance of antidiuretic hormone secretion) were compared between the two groups of patients [10, 11].

Statistical analysis

All clinical data collected in this research were entered into Excel database and analyzed by SPSS 21.0 statistical software independently by two groups of professional medical statisticians. Non-parametric tests were applied to two independent samples. The t test was conducted to test the measured data, and those in accordance with normal distribution are represented by mean ± standard deviation ($\bar{x}$ ± sd), expressed in t. Counting data was expressed in rate (%), using chi square test and Fisher exact probability method, expressed in Chi square. The rank sum test was used for ranked data, expressed in H. $P<0.05$ indicates the difference is statistically significant.

Results

Comparison of general data between two groups

The comparison of general data of the two groups was balanced and consistent, the difference was not statistically significant (all $P>0.05$) as shown in **Table 1**.

ICGA examination times and aneurysm clip adjustment

In the observation group, ICGA was performed 30 times during 26 cases of aneurysm clipping surgery, of which 23 cases of ICGA after aneurysms clipping has confirmed the complete clipping of aneurysm, and the parent artery was unobstructed and no stenosis was found. The remaining 3 cases did not reach expectations,

Table 2. Cases benefiting from ICGA

Case	Case 1	Case 2	Case 3
Perforating artery	Anterior choroidal artery	Recurrent artery	Posterior communicating artery
Aneurysm location	Posterior communicating artery aneurysm	Anterior communicating artery aneurysm	Posterior communicating artery aneurysm
ICGA time	3	2	2
The first ICGA condition	Posterior communicating artery stenosis	Residual aneurysm neck	Residual aneurysm neck
The last ICGA condition	No posterior communicating artery stenosis	Complete clipping of aneurysm	Complete clipping of aneurysm

Note: ICGA, indocyanine green fluorescein angiography.

Table 3. Comparison of the curative effect between two groups of patients

Group	Reoperation rate, n (%)	Hospitalization time (d)	GOS, n (%)		
			Good or mild paralysis	Severe paralysis	Plant life or death
Observation group (n=26)	0 (0.00)	15.12±5.85	25 (96.15)	1 (3.85)	0 (0.00)
Control group (n=26)	2 (7.69)	23.74±8.87	22 (84.62)	3 (11.54)	1 (3.85)
$t/X^2/H$	16.872	9.556	8.556	11.543	5.887
P	<0.001	<0.001	0.003	<0.001	0.012

Note: GOS, Glasgow coma scale.

Table 4. Comparison of the incidence of complications between two groups of patients, n (%)

Group	Pulmonary infection	Urinary tract infection	Gastrointestinal bleeding	Electrolyte disorders	Total incidence rate
Observation group (n=26)	1 (3.85)	1 (3.85)	0 (0.00)	0 (0.00)	2 (7.70)
Control group (n=26)	1 (3.85)	0 (0.00)	1 (3.85)	2 (7.70)	4 (15.40)
X^2					7.993
P					0.007

and ICGA showed satisfactory closure after aneurysm clip position adjustment or increased aneurysm clips. There was 1 case that underwent 3 ICGA procedures, and two cases that underwent ICGA twice as shown in **Table 2**.

The postoperative DSA follow-up examination showed no case of ischemic cerebral infarction.

Comparison of the curative effect between two groups of patients

The postoperative hospitalization time, reoperation rate, and postoperative GOS score were compared between two groups. The observation group was significantly superior to the control group, and the difference was statistically significant (all P<0.05) as shown in **Table 3**.

Comparison of the incidence of complications between two groups of patients

The incidence of complications in the observation group was significantly lower than that of the control group (7.70% vs. 15.40%), and the difference was statistically significant (P<0.05) as shown in **Table 4**.

Discussion

Intracranial aneurysm clipping surgery has characteristics of narrow visual field, complicated anatomical relationship with surrounding structures, and adjacent to vessels and important perforating vessels (anterior thalamic artery, recurrent artery, and posterior thalamic artery), which may cause intra-tumoral blood flow disorder etc. An improperly placed aneurysm clip might cause cerebral ischemia and infarction, and lead to postoperative delayed ischemic neurological dysfunction [12]. In addition, subjective factors such as insufficient surgical skill or lack of in-depth understanding of anatomical structure might be the cause of incomplete clipping of aneurysm and postoperative re-rupture and hemorrhage of residual tumor [13]. These are the main factors that affect the effect of surgery. Therefore, real-time monitoring and timely adjust the position of aneurysm clip during surgery becomes the main measure to protect the perforating artery.

Wu et al. stated that in their assessment of aneurysm surgery, 56% of the patients had perforating blood vessels [14]. Indocyanine green is a near-infrared fluorescent tricarbocyanine green dye, which can be rapidly combined with plasma globulin after injection into the blood. It can provide real-time blood flow information of intraoperative aneurysms, parent artery and surrounding related perforating artery after integration with surgical microscope [15]. In the study of evaluating cerebral blood flow by Roessler et al., the imaging time for all cases did not exceed 2 minutes [16]. Indocyanine green is rapidly metabolized by the

liver and was relatively safe. The incidence of side effects was 0.05%-0.21%, manifested as hypotension, arrhythmia, anaphylactic shock, nausea, itching, syncope, or rashes. In 2003, Özgiray et al. first reported application of ICGA in 20 cases of aneurysm patients during surgery and avoided 2 cases of aneurysm clipping insufficiency [17]. Xie et al. compared intraoperative ICGA and intraoperative DSA, among 123 cases of aneurysm surgery, intraoperative ICGA and DSA were consistent in 120 cases, and the coincidence rate was 97.5% [18, 19]. In this study, 26 patients in the observation group underwent ICGA 30 times during the aneurysm clipping surgery, of which 23 cases of ICGA after aneurysms clipping were confirmed to complete clipping of aneurysm. The parent artery was unobstructed and no stenosis was found. There were 2 cases underwent ICGA 2 times each, and 1 case underwent 3 times. The operation was completed with satisfactory clipping. Among them, 1 case of anterior communicating artery aneurysm and 1 case of posterior communicating artery aneurysm had residual aneurysm neck, and 1 case had posterior communicating artery stenosis. After the aneurysm clip was adjusted or additional aneurysm clip was added, ICGA showed good visualization of perforation, and there was no stenosis in the parent artery. No case of ischemic cerebral infarction was found in the head CT after surgery. In this way, severe neurological impairments such as limb dysfunction, emotional abnormalities, and cognitive impairments that may occur after surgery could be effectively avoided and safety can be improved.

With the application of intraoperative ICGA technique, the prognosis of patients undergoing craniotomy aneurysm clipping could be significantly improved. Schuette et al. compared the efficacy between patients with intraoperative ICGA and without ICGA, and found that intraoperative ICGA changed the surgical strategy of 15.32%, and significantly improved the patient's prognosis [20, 21]. In this research, the hospitalization time, reoperation rate, and GOS score of observation group were superior to those of control group. The incidence of complications in the observation group was significantly lower than that in the control group (7.70% vs. 15.40%), and the difference was statistically significant ($P<0.05$). The results were in accordance with a previous study [22]. Compared with the postoperative DSA review, even though incomplete aneurysm clipping or residual tumor was found after surgery, conservative treatment would be the most common choice if there are no clinical symptoms. However, this poses a great risk to the survival of patients, and if it can be detected in time using intraoperative ICGA, and this situation can be completely avoided [23]. However, ICGA has its limitations. Indocyanine green is poor in light transmittance and cannot show deep blood vessels in the cortex. It is only confined to the blood vessels within the scope of the microscope. The result of "false negative" is likely to occur when the arteriosclerosis of parent artery is severe and the thrombus at the neck of the tumor is formed. In addition, ICGA can only provide morphological images, and blood flow information cannot be quantitatively analyzed. Therefore, in the treatment of complex aneurysms, it is still necessary to combine intraoperative DSA, microvascular Doppler ultrasound, electrophysiological test and other detection methods.

In conclusion, ICGA provides a rapid and real-time visual assessment of aneurysm clipping and the opening conditions of parent artery and perforating artery during the surgery, so as to help reasonably adjust the clipping plan and improve prognosis.

Disclosure of conflict of interest

None.

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