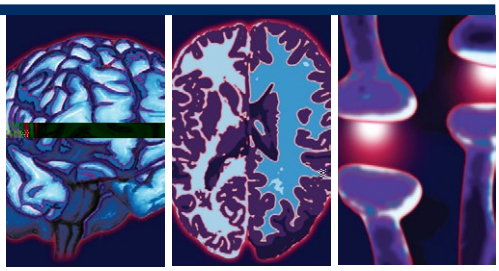

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Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder, which caused by inactivation of the tumour suppressor genes hamartin (TSC1) or tuberin (TSC2), and a ects approximately 1 in 6000 individuals per annum. About 85% of TSC patients manifesting with seizures that are often refractory to antiepileptic treatment [1]. Epilepsy surgery in patients with apparently focal epilepsy may be a good option. However, some TSC patients are with refractory epilepsy involving eloquent areas, which made these patients poor candidates by routine operation. Combined multiple subpial transections (MST) and resection has been demonstrated to improve seizure control in patients with multifocal epilepsy involving eloquent cortex [2], including one patient with TSC-associated epilepsy [3], without inducing signi cant functional de cits.

We have previously developed and applied a new method in the treatment of epilepsy speci cally located in eloquent areas, which was called bipolar electro-coagulation on functional cortex (BCFC) [4-7]. Our results demonstrated that in some cases, when the epileptogenic foci were located in a functional cortex, the combined therapy of non-eloquent foci resection and BCFC was proved e ective and greatly improved the outcome of the surgery [4,5]. In the utmost recent study we demonstrated that the BCFC technique was really e ective and safe, without resulting in permanent neurological de cits in the treatment of unifocal epilepsy involving eloquent areas [6,7].

e combined foci resection and BCFC in the treatment of TSC patients with refractory epilepsy involving eloquent has not been reported so far. Here, we retrospectively reviewed all data of the 10 patients who were diagnosed with TSC and underwent the combined foci resection and BCFC at the Beijing Sanbo Brain Hospital and Beijing Sanbo Fuxing Brain Hospital between May 2004 and May 2014.

Methods

■ Patients

Ten patients who were diagnosed as TSC with epilepsy involving eloquent and non-eloquent cortex were included in this study, who underwent resection with BCFC at Beijing Sanbo Brain Hospital and Beijng Sanbo Fuxing Brain Hospital from May 2004 to May 2014 and followed up for 30 to 72 (mean 49.5) months.

ere were ve males and ve females, aged 10-35 years, with a mean age of 18.1 years. ey had 14.9 years of recorded preoperative history of epilepsy on average.

Seizure types included complex partial seizures (CPS), simple partial seizures (SPS), generalized tonic-clonic seizure (GTCS) and secondary generalized tonic-clonic seizure (SGTCS). All the Ten patients underwent CT, MRI and video scalp electroencephalography (EEG) monitoring as pre-surgical evaluation. Additionally, Eight and seven patients received magnetoencephalography (MEG) and intracranial EEG (invasive monitoring), respectively.

Surgical Procedure

e motor, sensory cortices and epileptogenic foci were identi ed with cortical stimulation in order to address the epileptogenci regions located in the eloquent and non-eloquent areas. At rst, pre-resection electrocoticography (EcoG) was performed. en after resection of non-functional epileptogenic cortices, ECoG **(Fig. e 1)** was performed in functional epileptogenic regions before BCFC [4-6]. BCFC was applied over the arachnoid membrane with an output power of 4-5W. e brain surface was kept clean and moist with the saline gauze. ere was 45 degree angle between the forceps axis and the brain surface. e direction of electro-coagulation was perpendicular to the long axis of brain gyrus. e tip diameter of the bipolar forceps was 2mm. is procedure was performed at an interval of 5mm and with 1 second duration.

e brain surface was washed immediately with the saline to lower the brain temperature released by electro-coagulation. Following the BCFC procedure, post-BCFC ECoG was performed **(Fig. e 2)**. e output power never exceeded

5W because higher output power may damage the internal pyramidal layer and may result in unacceptable neurological de cits

Red and white stripes at regular intervals were clearly visible on the electro-coagulated cortex. e BCFC was applied over outside arachnoid mater and the blood vessels located in pial mater remained undamaged except for the capillaries, After BCFC, the arti cial dura was covered on the cortex, which can signi cantly reduce the occurrence of adhesions and epilepsy.

Results

■ Follow-up

1. e mean duration of postoperative follow-up was 49.5 months (ranged 30-72 months). e outcome of Engel class I was achieved in 5 patients, Engel class II in 3 patients and Engel class III in 2 patients, respectively.
2. Follow-up MRI was performed on the ten patients 1 to 3 years after surgery, showing no abnormality in all the patients **(Fig. e 3)**.
3. Neuropsychological evaluation was performed just before surgery, 6 months after surgery and 2 years after surgery and the postoperative intelligence and memory scores were e ectively improved according to Wechsler Adult Intelligence Scale-Revised in China or Wechsler intelligence scale for children-Revised in China (WAIS-RC or WISC-RC)

Figure 1: ECoG before BCFC: reveals multiple spikes and slow waves in the central cortex.

Figure 2: ECoG after BCFC: reveals discharge disappear.

and Wechsler Memory Scale-Revised in China (WMS-RC) evaluation (Tab e 1).

4. Complications: One patient developed mild hemiparesis after BCFC and was fully recovered within 1 month. No occurrences of hemiparesis, hemorrhage or infection. No permanent neurological de cit was found for all the patients by a standard clinical examination.

Discussion

TSC-associated epilepsy generally onsets after birth, and is often refractory to antiepileptics, surgical management of intractable epilepsy with TSC is usually restricted to the patients having epileptogenic foci associated with tuber located in non-eloquent areas of the cortex [8-14].

ese results are generally very satisfactory after complete resection of the epileptogenic tuber [13]. Tailored surgical resection of epileptogenic foci has been reported to stop seizures in 57% of drug-resistant patients and decreased seizures frequency more than 90% [15]. But resection to an epileptogenic tuber overlapped by functionally cortical cortices might be unacceptable because of

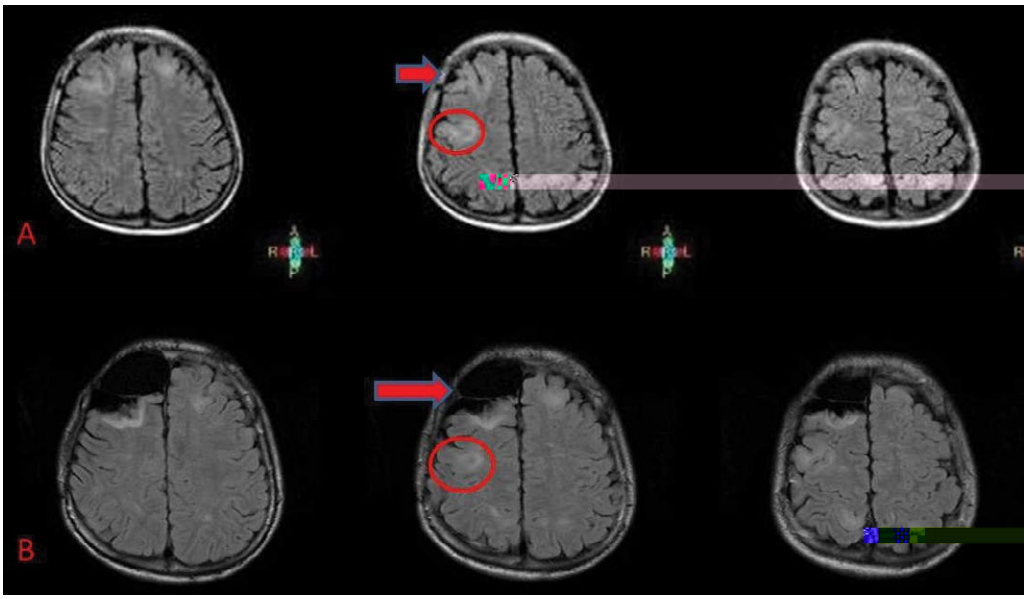

Figure 3: Epileptogenci regions located in the eloquent and non-eloquent areas.
A: The imaging before BCFC and resection
B: The imaging after 1 year of BCFC and resection: no significant changes in coagulated area
Red arrow: removal of nodules
Red circle: coagulated nodules

Table 1: Neuropsychological evaluation of the ten patients with TSC before and after epilepsy surgery.

No. of patients	Just before surgery		6 months after surgery		2 years after surgery	
	FIQ	MQ	FIQ	MQ	FIQ	MQ
1	81	71	86	80	90	85
2	62	58	68	65	75	70
3	93	84	90	82	92	84
4	66	46	69	52	77	60
5	50	40	52	36	49	42
6	55	46	59	51	67	60
7	65	60	67	70	74	78
8	70	63	72	68	76	79
9	64	62	69	71	74	80
10	57	49	63	54	70	62

FIQ: full intelligence quotient; MQ: memory quotient

high risk of neurological de cits. It is commonly recommended that patients with multiple and bilateral epileptogenic foci are not amenable to resection surgery, especially involving the eloquent cortex [16]. With the consideration of MST interrupting horizontal synchronizing neuronal networks while preserving vertical functional units, and MST was rstly introduced to treat epilepsy originating from functional cortex by Morrell [17]. Placement of pure MST over the sensorimotor cortex has been shown to produce a clean electrocorticogram with long-lasting seizure remission [18].

ere is almost no literature to report the treatment of TSC-associated epilepsy involving eloquent cortex with MST. Only Romanelli P reported that one patient who was TSC-associated epilepsy associated with multifocal epileptogenic foci involving eloquent cortex achieved a favorable outcome after underwent combination of MST and resective surgery [3].

e other reports on the e cacy of pure MST or resection with MST are di erent widely. Je rey P. Blount reported that 12 (46%) patients were seizure free (Engel Class I), 11 (42%) patients achieved Engel Class II and III in 26 patients who underwent cortical resection with MST [19]. Susan S. Spencer reported that of 12 subjects who underwent pure MST or resection and MST, ve (42%) patients obtained a signi cant improvement in seizure frequency and two patients had a marked decrease in the severity of their seizures [20]. Orrin Devinsky also reported that 10 (77%) patients of 13 were improved by MST and resection [21].

BCFC is a new surgical technique that can reduce the cortex-related seizures as a result of destructing the epileptic foci and transmission by thermal energy, which is applied with bipolar coagulation forceps. e mechanism underlying BCFC in treating epilepsy is presumed to have a similar principle as MST. Our previously clinical trials have demonstrated that the electro-coagulation with output power on 4-5W can damage the external molecular layer, external granular layer, and the external pyramidal layer (only reaches to the third layer of the cortex), without decaying the internal pyramidal layer (Fig. e 4). e surgical procedure is safe without leading to unacceptable neurological de cits [4-7]. e pure BCFC technique has showed good e cacy to treat refractory epilepsy as the

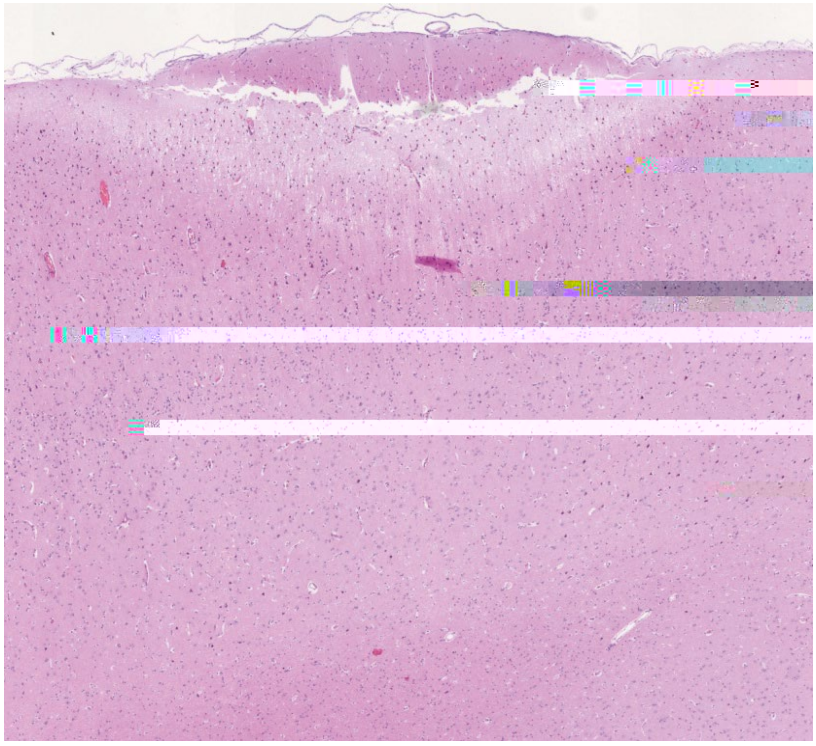

Figure 4: Epileptogenci regions located in the eloquent and non-eloquent areas.

After BCFC, the molecular layer of the cerebral cortex and the superficial external granular layer were coagulated and denatured, and the granular layer and the outer vertebral body of the brain tissue were edematous. HE x 40.

epileptogenic foci is located in the eloquent [6]. When epileptogenic focus overlaps the eloquent cortex, the approach of combination of resection and BCFC can safely produce ablation of the epileptogenic focus [4-6]. Our previous study also showed that lesionectomy combined with BCFC (71 patients) was signi cantly more e ective than lesionectomy only (78 patients) with the 2-5 years of follow-up [5,6].

In general, compared with lesionectomy with MST, the outcome and complications of BCFC with lesionectomy are similar. On the one hand, BCFC was applied over the arachnoid membrane; On the other hand, BCFC causes thermal injury, while MST leads to mechanical injury. erefore, the complications of BCFC are less severe.

e approach of foci resection combined with BCFC to manage the TSC-associated refractory epilepsy has not been reported so far. Our ten cases had an excellent outcome that the morphology of these coagulated areas showed no signi cant changes by MRI, and their postoperative intelligence and memory scores were improved to some extent and without serious complications after combination of resection and BCFC of epileptogenic foci involving the eloquent cortex. According to our experience, the approach of foci resection combined with BCFC could be regarded as one of the e ective and reliable method of therapy for TSC-associated refractory epilepsy involving eloquent. e reasons are as follows:

i. Localization-related refractory epilepsy involving eloquent and non-eloquent cortex made these TSC patients poor candidates for conventional resection surgery [16];

ii. Seizure-free status is very rare in vagus nerve stimulation and disconnecting the corpus callous for TSC-associated refractory epilepsy[19];

iii. Our previous study proved the safety, ef- cacy, and convenience of handling the BCFC technique to treat drug-resistant seizures[7];

iv. e approach of combination of resection and BCFC can safely produce ablation of the epileptogenic focus when ictal onset overlaps the eloquent cortex [4,5].

v. Compared with MST, the complications of BCFC seem less severe.

Although the BCFC technique is only a palliative surgery and cannot be applied for all epilepsies [7], and long-term follow-up studies of international multicenter are required to delineate further e ects, the combination therapy of foci resection and BCFC to manage the TSC-related epilepsy involving eloquent cortex holds signi cant promise for future therapy.

e approach of foci resection with BCFC is a new and e ective method and can meaningfully manage the TSC-associated refractory epilepsy involving eloquent areas without permanent neurological de cit. Prospective randomized studies are needed.

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Conflict of interest

None of the authors has any con ict of interest to disclose.

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