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Judul Artikel : **Hemispherotomy for drug-resistant hemispheric epilepsy in Indonesian population**

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Journal: Epilepsy & Behavior Reports

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Manuscript Details

Manuscript number	EBCR_2019_110_R1
Title	Hemispherotomy for Drug-resistant Hemispheric Epilepsy in Indonesian Population
Article type	Original Research Article

Abstract

ABSTRACT Background: Hemispherotomy is a surgical treatment indicated in drug-resistant epilepsy with unilateral hemispheric pathology. Hemispherotomy is less invasive compared to hemispherectomy. Aim: We are discussing our experience performing hemispherotomy in selected cases and presenting the result of this relatively uncommon procedure in our centers in Indonesia. Methods: This is a retrospective observational study conducted from 1999 to July 2019 in two epilepsy neurosurgical centers in Semarang, Indonesia. Surgical techniques included vertical parasagittal approach (VPH), peri-insular hemispherotomy (PIH) and modified PIH called Shimizu approach (SA). The postoperative assessment was carried out using seizure outcome parameters of Engel. Results: Seizure freedom (Engel class I) outcome was achieved in 10 patients (62.5%), class II in 3 patients (18.7%), class III in 2 patients (12.5%), and class IV in 1 patient (6.3%) with follow-up duration spanning from 24 to 160 months. Conclusion: Our series is the most extensive documentation of hemispherotomy in Indonesian population with Engel class I rate 62.5%, and 81.3% of patients showed improved symptoms.

Keywords	epilepsy; drug-resistant; hemispherotomy

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Cover Page

August, 5th 2019

Editorial Department of Epilepsy and Behavior Case Report

Dear Editor of Epilepsy and Behavior Case Report,

I am submitting a manuscript for consideration of publication in Epilepsy and Behavior Case Report. The manuscript is entitled "Hemispherotomy for Intractable Hemiplegic Epilepsy in Indonesian Population".

It has not been published elsewhere and that it has not been submitted simultaneously for publication elsewhere. Hemispherotomy is a surgical procedure of hemispheric disconnection with good seizure-free outcomes to treat intractable infantile hemiplegic epilepsy and has a lower rate of postoperative complications compared to hemispherectomy. Seizure freedom (Engel class I) outcome was achieved in 10 patients (62.5%), class II in 3 patients (18.7%), class III in 2 patients (12.5%), and class IV in 1 patient (6.3%) with follow-up duration spanning from 24 to 160 months.

All authors declare no conflict of interest regarding the publication of this article.

Thank you very much for your consideration.

Yours Sincerely,

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Hemispherotomy for Drug-resistant Hemispheric Epilepsy in Indonesian Population

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Background: Hemispherotomy is a surgical treatment indicated in drug-resistant epilepsy with unilateral hemispheric pathology. Hemispherotomy is less invasive compared to hemispherectomy.

Aim: We are discussing our experience performing hemispherotomy in selected cases and presenting the result of this relatively uncommon procedure in our centers in Indonesia.

Methods: This is a retrospective observational study conducted from 1999 to July 2019 in two epilepsy neurosurgical centers in Semarang, Indonesia. Surgical techniques included vertical parasagittal approach (VPH), peri-insular hemispherotomy (PIH) and modified PIH called Shimizu approach (SA). The postoperative assessment was carried out using seizure outcome parameters of Engel.

Results: Seizure freedom (Engel class I) outcome was achieved in 10 patients (62.5%), class II in 3 patients (18.7%), class III in 2 patients (12.5%), and class IV in 1 patient (6.3%) with follow-up duration spanning from 24 to 160 months.

Conclusion: Our series is the most extensive documentation of hemispherotomy in Indonesian population with Engel class I rate 62.5%, and 81.3% of patients showed improved symptoms.

Keywords: epilepsy, drug-resistant, hemispherotomy

Dear Editor of Epilepsy & Behaviour Reports,

We would like to thank the editor and reviewers for their comments, critics, and suggestions in improving this manuscript.

Thank you very much.

Best regards,

Muhamad Thohar Arifin, MD, PhD

Department of Neurosurgery

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Semarang, INDONESIA

Comments from the editors and reviewers:
-**Editor**

-
-**Reviewer 1**

-

This is a case series of 18 hemispherotomy patients from Indonesia, primarily reporting seizure outcomes. Several concerns also need to be addressed before this manuscript has any meaningful message for the epilepsy community:

1. Authors should clarify how this series is different from other case series of hemispheric surgery reported from Asia including up to 129 patients (for example: Dagar et al. Pediatr Neurosurg. 2011;47(3):186-93.), other than just the country of origin.

   Our series reported only hemispherotomy case in Indonesia (24 from 723 cases), while we believe that the reported patients by Dagar et al., included all epilepsy cases. We believe that this report is useful to evaluate the outcome of epilepsy surgery in a developing country, especially in treating rarer cases. This information might complement the global data of epilepsy surgery report and thus might be useful in determining the strategy to improve the epilepsy surgery services in our country and region.

2. The methods section is severely lacking in details. What was their decision process for hemispheric surgery? How was seizure frequency ascertained? Was there a systematic evaluation for post-op complications? What were the MRI findings? Was there imaging evidence for normality of hemisphere contralateral to the one operated?

   We have included the imaging of one case who underwent hemispherotomy. The decision to proceed to hemispherotomy was determined by the consensus among epileptologist, epilepsy neurosurgeon, and neuropsychologist.

3. The variability in the time for measuring seizure outcomes is an important confounding factor. The primary outcome should be Engel class at 1 year follow up. Patients with <1 year follow up should be omitted. Engel outcomes for patients with longer follow up can be reported as secondary outcomes.

   For outcome result, we only included patients with follow-up duration longer than 12 months, although we listed all patients operated until July 2019.

4. The low proportion of class I outcomes seen in this study need to be explained. What was the role of patient selection criteria in driving outcomes?

   We repeated the follow-up to the patients by phone calls and the result of Engel Class I has been changed according to the latest follow-up. The result of Engel Class I outcome has been improved.

5. In the methods section, authors report measuring “motoric” outcome. What is this? How was it measured? I do not see it reported in the results.

   We decided to focus on the seizure frequency outcome, as it was impossible to assess the motoric outcome via indirect interview.

6. In the results section, authors mention that 1 patient developed “temporary preserved symptom”. What is this?

   We have revised the sentence to avoid confusion.

7. It may be desirable to remove the single patient with VPH, so that the series is more homogeneous.

   Our aim is to inform the international society that we have performed hemispherotomy in Indonesia. As there is no statistical evaluation in this

study, we decided to include all patients with any approach, including VPH.

8. Methods, results, and discussion are all mixed up. For example, the patients characteristics described in methods section should be a part of results. In the subsection on surgical procedure, I do not think that the outcomes reported for SA (75% of 12 patients) is from authors work. This should be in discussion section. Similarly the discussion on indications of VPH should be moved to discussion section from methods.

   We have revised the methods, results, and discussion sections.

9. Introduction section: the distinction made by authors into “acquired” and “congenital” lesions is unclear.

   We have revised the sentence.

-**Reviewer 2**

-

Figure of a patient MRI showing one such case pre and post surgery (if possible one with each approach or at least one).

This is overall a good study to show the center specific data on hemispherotomy of 18 patients. Written very well and to the point. Some minor revision are suggested

1. If authors can add a MRI figure of a patient pre and post surgery, this will add to understanding of procedure. Since PIH is the most common procedure, to show one such example.

We have provided the figure of a case operated with PIH.

2. Under Methods: Surgical procedure para3 last line- if can rewrite to mention: in a prior study this approach...(it is confusing with % and number if this is of your study vs prior)...

We have edited the methods section.

3. Results section- outcomes para line 4: replace on with in (4 patients). And line 5: if can explain temporary preserved symptom...

We have deleted the sentence to avoid confusion.

4. Discussion para 2 line 10- replace from to "of the"... In our case, from 11 to - In our case, of the 11

Sentence edited.

(also following this para if authors can add 2-3 line mentioning why in their center seizure free outcome was lower compared to prior studies)

We repeated the follow-up to the patients by phone calls, and the result of Engel Class I has been changed according to the latest follow up.

5. Discussion last para- line 5: change underwent to 'that underwent'

Sentence edited.

Editor-in-Chief

Please ensure English and references are carefully reviewed for correctness.

Use "drug-resistant" for intractable/refractory/pharmaco-resistant; "anti-seizure drug" for antiepileptic drug.

We have revised the terms.

Hemispherotomy for Drug-resistant Hemispheric Epilepsy in Indonesian Population

ABSTRACT

Background: Hemispherotomy is a surgical treatment indicated in drug-resistant epilepsy with unilateral hemispheric pathology. Hemispherotomy is less invasive compared to hemispherectomy.

Aim: We are discussing our experience performing hemispherotomy in selected cases and presenting the result of this relatively uncommon procedure in our centers in Indonesia.

Methods: This is a retrospective observational study conducted from 1999 to July 2019 in two epilepsy neurosurgical centers in Semarang, Indonesia. Surgical techniques included vertical parasagittal approach (VPH), peri-insular hemispherotomy (PIH) and modified PIH called Shimizu approach (SA). The postoperative assessment was carried out using seizure outcome parameters of Engel.

Results: Seizure freedom (Engel class I) outcome was achieved in 10 patients (62.5%), class II in 3 patients (18.7%), class III in 2 patients (12.5%), and class IV in 1 patient (6.3%) with follow-up duration spanning from 24 to 160 months.

Conclusion: Our series is the most extensive documentation of hemispherotomy in Indonesian population with Engel class I rate 62.5%, and 81.3% of patients showed improved symptoms.

Keywords: epilepsy, drug-resistant, hemispherotomy

INTRODUCTION

Hemispherotomy is a surgical treatment indicated in drug-resistant epilepsy with unilateral hemispheric pathology.[1] Patients with drug-resistant hemispheric epilepsy are potential candidates for this procedure.[2] The underlying etiology for such condition may include acquired lesions (e.g., Rasmussen's encephalitis, Sturge-Weber-syndrome, porencephaly, and perinatal stroke) or disturbance in neuronal migration (e.g., hemimegalencephaly, cortical dysplasia, and hemiconvulsion-hemiplegia-epilepsy syndrome).[3,4]

As it does not involve cerebral arteries ligation and hemisphere removal, hemispherotomy has relatively lower complications compared to more invasive hemispherectomy which may result in more hemorrhage, hydrocephalus, subdural fluid collections, and cerebral hemosiderosis.[5,6] In functional hemispherotomy, connections between hemispheres are disturbed without severing the vascularization of either hemisphere. Since its first description, there have been two major techniques for hemispherotomy: the vertical parasagittal hemispherotomy (VPH), initially described by Delalande[7,8] and the peri-insular hemispherotomy (PIH) by Villemure.[9,10] Other authors have described modifications of either approach, including PIH modification by Shimizu and Maehara[11] who reported satisfactory results.[12]

We are discussing our experience performing hemispherotomy in selected cases and presenting the result of this relatively uncommon procedure in our centers. To our best knowledge, this is the most extensive report of hemispherotomy documentation for drug-resistant epilepsy in Indonesia.

METHODS

Settings: This study is a retrospective observational study based on medical records in two epilepsy centers (Department of Neurosurgery Kariadi and Telogorejo Hospital) in Semarang, Indonesia. We observed the patients with drug-resistant seizure who underwent hemispherotomy from 1999 to July 2019. This study has been ethically approved by the institution review board.

Presurgical and surgical consideration: Pre-surgical evaluation included review of history and physical examination findings, seizure semiology, scalp-EEG recordings, and brain magnetic resonance imaging (MRI). Each patient underwent a pre-surgical evaluation, and the decision to proceed with hemispherotomy was made by consensus among epileptologists, neurosurgeons, and a neuropsychologist. The consideration to perform either VPH or PIH approach (including PIH modification called Shimizu's approach [SA]) was decided based on the underlying pathology and clinical judgment. All surgeries were performed by an epilepsy neurosurgeon (Z.M.).

PIH is composed of three main steps: the supra-insular window, infra-insular window, and insular resection. Callosotomy is performed from the supra-insular window via the frontal and parietal

cortex (cortico-thalamic tract) which is then extended posteriorly to the hippocampal tail and anteriorly to the fronto-basal portion anterior to basal ganglia. Mesial temporal resection is done via the infra-insular window. Insular resection is performed by subpial aspiration or undermined by incising at the level of the claustrum.[10]

In SA, the frontal operculum was resected en bloc including the upper half of insula. The callosotomy is performed through the lateral ventricle. The resection cavity is communicated to the inferior ventricle, and the medial temporal structures are resected. In the final step, the horizontal fibers emerging from the frontal lobe are sectioned along the posterior edge of the minor wing of the sphenoid bone.

The indications for VPH include the presence of ventriculomegaly and the distance between the vertex and temporal horn. One author favored VPH if the distance was less than 10 cm or in small children as the incision was smaller compared to PIH.[13]

Postoperative assessment: The primary outcome of this study was the postsurgical seizure outcome (baseline 12 months). Seizure outcome was assessed with Engel's parameters[14]: class I (free of disabling seizures), class II (rare disabling seizures), class III (worthwhile improvement) and class IV (no worthwhile improvement). The outcome was documented on the patient's last visit or through phone calls interview.

RESULTS

Demography of patients: Twenty-four hemispherotomies were performed from 723 cases operated for drug-resistant epilepsy (see table 1). Patients' age at surgery ranged from 2 to 28 years old (mean 12.82±6.3 years) with 11 males and 13 females. The onset of seizure started from 0 to 7 years old (mean 2.08±2.1 years). The seizure frequency ranged from 1 to 2 episodes per month to more than 20 episodes daily. Twelve patients had right-sided weakness, 11 had left-sided weakness, and 1 had bilateral hemiplegia.

Surgical procedure and underlying pathology: The underlying pathology was congenital porencephaly in 12 cases, hemispheric hemiatrophy in 4, Rasmussen's encephalitis in 2, hemimegalencephaly in 1, middle cerebral artery (MCA) infarction in 1, polymicrogyria in 1, hemispheric encephalomalacia in 1, Sturge-Weber syndrome in 1, and mesial temporal sclerosis (MTS) with bilateral encephalomalacia in 1 patient. Only one patient was operated with VPH approach while the rest (23 cases) underwent PIH, including 4 cases treated with SA. Thirteen patients were operated from the left side, including one patient with bilateral hemiplegia.

Outcomes: Seizure freedom (Engel class I) outcome was achieved in 10 patients (62.5%), class II in 3 patients (18.7%), class III in 2 patients (12.5%), and class IV in 1 patient (6.3%) with follow-up duration spanning from 24 to 160 months. Among eight patients without Engel class, six had less than 12 months of follow-up, while two had inadequate follow-up records. We reported transient worsening hemiparesis in five patients, who subsequently underwent physiotherapy and showed improvement. Neither major complication nor postoperative mortality was reported.

DISCUSSION

We documented the most extensive study regarding hemispherotomy performed to treat drug-resistant epilepsy in Indonesia with follow up duration reaching more than five years. Since hemispherotomy is a relatively rare procedure, we only observed 24 cases from more than 700 cases operated in our centers. This figure is almost similar to other reports. [13,15]

Hemispherotomy is mainly indicated for drug-resistant infantile hemispheric epilepsy. Most of our patients had a unilateral weakness with various severity (87.5%), although hemianopsia symptom was not documented. The seizure-free (Engel class I) outcome of hemispherotomy is considered good with reported outcome varied from 68-94%.[13] In our study, 10 (62.5%) patients had Engel class I outcome, while generally, 13 (81.3%) patients were having improvement (Engel class I and II). The seizure-free outcome in PIH was reported to be 90% in a 9-year follow-up period[10], while the seizure free outcome in VPH was reported to be 74%[8], however, both authors stated that the underlying etiology may influence the success of the surgery. The remarkable outcome was reported in 75% of 12 patients treated with SA.[12] In this series, of the 10 patients

Engel Class I, 9 were operated with PIH approach while 1 underwent SA surgery. We also documented the only VPH in a 6-year-old girl with Sturge-Weber syndrome.

Acquired lesions such as porencephaly were known to have a better prognosis, along with Rasmussen's encephalitis and Sturge-Weber syndrome compared to neuronal migration defects like cortical malformation due to suspected involvement of the contralateral hemisphere.[8] Also, patients with cortical malformations tend to be operated at a younger age. Poor prognosis predictors include contralateral abnormality and abnormal hemispheres with extensive insular and subcortical heterotopic gray matter in imaging studies.[16-17] In this series, among patients with seizure freedom, 6 (60%) was diagnosed with porencephaly, 2 with hemispheric hemiatrophy, 1 with Rasmussen's encephalitis, and 1 with large MCA infarction.

Seizure frequency reduction may improve the quality of life of patients and cognitive capability. The delayed surgical procedure from the age of onset is associated with general outcomes, especially in verbal communication ability.[18] The average delay of surgery in our cases was 10.43±5.9 years (range 2 - 23 years), with an average onset of seizure started from 0 to 7 years old (mean 2.08±2.1 years).

Compared to anatomical and functional hemispherectomy, modified PIH had less risk of surgical complications and reoperation rate, although the seizure outcome did not significantly differ between techniques[6]. Hydrocephalus is a common sequel after hemispherectomy and is strongly correlated with anatomical hemispherectomy.[19] Transient postoperative hemiparesis or hemiplegia is also seen in most patients that underwent hemispherotomy; however, this phenomenon does not last in the long term.[18] In our series, five patients developed temporary worsening hemiparesis, which we promptly treated.

CONCLUSION

Hemispherotomy is a surgical procedure of hemispheric disconnection with good seizure-free outcomes to treat drug-resistant infantile hemispheric epilepsy and has a lower rate of postoperative complications compared to hemispherectomy. Our series is the most extensive

documentation of hemispherotomy in Indonesian population with Engel class I rate 62.5%, and 81.3% of patients showed improved symptoms.

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Hemispherotomy for Intractable Hemiplegic Epilepsy in Indonesian Population

Muhamad Thohar Arifin[1], Zainal Muttaqin[1], Yuriz Bakhtiar[1], Erie Andar[1], Dody Priambada[1], Happy Brotoarianto[1], Ajid Risdianto[1], Krisna Prihastomo[1], Gunadi Kusnarto[1], Jacob Bunyamin[1]

[1]Department of Neurosurgery Kariadi Hospital Diponegoro University, Semarang, Indonesia

HIGHLIGHTS

- Hemispherotomy is a surgical procedure of hemispheric disconnection with good seizure-free outcomes to treat intractable infantile hemiplegic epilepsy and has a lower rate of postoperative complications compared to hemispherectomy.
- We are discussing our experience performing hemispherotomy in selected cases and presenting the result of this relatively uncommon procedure in our centers
- To our best knowledge, this is the largest report of hemispherotomy documentation for intractable epilepsy in Indonesia.
- Engel class I outcome was seen in 4 (22.2%) patients, class II in 7 (38.9%) patients, class III in 4 (22.2%) patients, and class IV in 1 (5.6%) patient assessed at 6 to 68 months of follow-up.

Hemispherotomy for Drug-resistant Hemispheric Epilepsy in Indonesian Population

ABSTRACT

Background: Hemispherotomy is a surgical treatment indicated in drug-resistant epilepsy with unilateral hemispheric pathology. Hemispherotomy is less invasive compared to hemispherectomy.

Aim: We are discussing our experience performing hemispherotomy in selected cases and presenting the result of this relatively uncommon procedure in our centers in Indonesia.

Methods: This is a retrospective observational study conducted from 1999 to July 2019 in two epilepsy neurosurgical centers in Semarang, Indonesia. Surgical techniques included vertical parasagittal approach (VPH), peri-insular hemispherotomy (PIH) and modified PIH called Shimizu approach (SA). The postoperative assessment was carried out using seizure outcome parameters of Engel.

Results: Seizure freedom (Engel class I) outcome was achieved in 10 patients (62.5%), class II in 3 patients (18.7%), class III in 2 patients (12.5%), and class IV in 1 patient (6.3%) with follow-up duration spanning from 24 to 160 months.

Conclusion: Our series is the most extensive documentation of hemispherotomy in Indonesian population with Engel class I rate 62.5%, and 81.3% of patients showed improved symptoms.

Keywords: epilepsy, drug-resistant, hemispherotomy

INTRODUCTION

Hemispherotomy is a surgical treatment indicated in drug-resistant epilepsy with unilateral hemispheric pathology.[1] Patients with drug-resistant hemispheric epilepsy are potential candidates for this procedure.[2] The underlying etiology for such condition may include acquired lesions (e.g., Rasmussen's encephalitis, Sturge-Weber-syndrome, porencephaly, and perinatal stroke) or disturbance in neuronal migration (e.g., hemimegalencephaly, cortical dysplasia, and hemiconvulsion-hemiplegia-epilepsy syndrome).[3,4]

As it does not involve cerebral arteries ligation and hemisphere removal, hemispherotomy has relatively lower complications compared to more invasive hemispherectomy which may result in more hemorrhage, hydrocephalus, subdural fluid collections, and cerebral hemosiderosis.[5,6] In functional hemispherotomy, connections between hemispheres are disturbed without severing the vascularization of either hemisphere. Since its first description, there have been two major techniques for hemispherotomy: the vertical parasagittal hemispherotomy (VPH), initially described by Delalande[7,8] and the peri-insular hemispherotomy (PIH) by Villemure.[9,10] Other authors have described modifications of either approach, including PIH modification by Shimizu and Maehara[11] who reported satisfactory results.[12]

We are discussing our experience performing hemispherotomy in selected cases and presenting the result of this relatively uncommon procedure in our centers. To our best knowledge, this is the most extensive report of hemispherotomy documentation for drug-resistant epilepsy in Indonesia.

METHODS

Settings: This study is a retrospective observational study based on medical records in two epilepsy centers (Department of Neurosurgery Kariadi and Telogorejo Hospital) in Semarang, Indonesia. We observed the patients with drug-resistant seizure who underwent hemispherotomy from 1999 to July 2019. This study has been ethically approved by the institution review board.

Presurgical and surgical consideration: Pre-surgical evaluation included review of history and physical examination findings, seizure semiology, scalp-EEG recordings, and brain magnetic resonance imaging (MRI). Each patient underwent a pre-surgical evaluation, and the decision to proceed with hemispherotomy was made by consensus among epileptologists, neurosurgeons, and a neuropsychologist. The consideration to perform either VPH or PIH approach (including PIH modification called Shimizu's approach [SA]) was decided based on the underlying pathology and clinical judgment. All surgeries were performed by an epilepsy neurosurgeon (Z.M.).

PIH is composed of three main steps: the supra-insular window, infra-insular window, and insular resection. Callosotomy is performed from the supra-insular window via the frontal and parietal

cortex (cortico-thalamic tract) which is then extended posteriorly to the hippocampal tail and anteriorly to the fronto-basal portion anterior to basal ganglia. Mesial temporal resection is done via the infra-insular window. Insular resection is performed by subpial aspiration or undermined by incising at the level of the claustrum.[10]

In SA, the frontal operculum was resected en bloc including the upper half of insula. The callosotomy is performed through the lateral ventricle. The resection cavity is communicated to the inferior ventricle, and the medial temporal structures are resected. In the final step, the horizontal fibers emerging from the frontal lobe are sectioned along the posterior edge of the minor wing of the sphenoid bone.

The indications for VPH include the presence of ventriculomegaly and the distance between the vertex and temporal horn. One author favored VPH if the distance was less than 10 cm or in small children as the incision was smaller compared to PIH.[13]

Postoperative assessment: The primary outcome of this study was the postsurgical seizure outcome (baseline 12 months). Seizure outcome was assessed with Engel's parameters[14]: class I (free of disabling seizures), class II (rare disabling seizures), class III (worthwhile improvement) and class IV (no worthwhile improvement). The outcome was documented on the patient's last visit or through phone calls interview.

RESULTS

Demography of patients: Twenty-four hemispherotomies were performed from 723 cases operated for drug-resistant epilepsy (see table 1). Patients' age at surgery ranged from 2 to 28 years old (mean 12.82±6.3 years) with 11 males and 13 females. The onset of seizure started from 0 to 7 years old (mean 2.08±2.1 years). The seizure frequency ranged from 1 to 2 episodes per month to more than 20 episodes daily. Twelve patients had right-sided weakness, 11 had left-sided weakness, and 1 had bilateral hemiplegia.

Surgical procedure and underlying pathology: The underlying pathology was congenital porencephaly in 12 cases, hemispheric hemiatrophy in 4, Rasmussen's encephalitis in 2, hemimegalencephaly in 1, middle cerebral artery (MCA) infarction in 1, polymicrogyria in 1, hemispheric encephalomalacia in 1, Sturge-Weber syndrome in 1, and mesial temporal sclerosis (MTS) with bilateral encephalomalacia in 1 patient. Only one patient was operated with VPH approach while the rest (23 cases) underwent PIH, including 4 cases treated with SA. Thirteen patients were operated from the left side, including one patient with bilateral hemiplegia.

Outcomes: Seizure freedom (Engel class I) outcome was achieved in 10 patients (62.5%), class II in 3 patients (18.7%), class III in 2 patients (12.5%), and class IV in 1 patient (6.3%) with follow-up duration spanning from 24 to 160 months. Among eight patients without Engel class, six had less than 12 months of follow-up, while two had inadequate follow-up records. We reported transient worsening hemiparesis in five patients, who subsequently underwent physiotherapy and showed improvement. Neither major complication nor postoperative mortality was reported.

DISCUSSION

We documented the most extensive study regarding hemispherotomy performed to treat drug-resistant epilepsy in Indonesia with follow up duration reaching more than five years. Since hemispherotomy is a relatively rare procedure, we only observed 24 cases from more than 700 cases operated in our centers. This figure is almost similar to other reports. [13,15]

Hemispherotomy is mainly indicated for drug-resistant infantile hemispheric epilepsy. Most of our patients had a unilateral weakness with various severity (87.5%), although hemianopsia symptom was not documented. The seizure-free (Engel class I) outcome of hemispherotomy is considered good with reported outcome varied from 68-94%.[13] In our study, 10 (62.5%) patients had Engel class I outcome, while generally, 13 (81.3%) patients were having improvement (Engel class I and II). The seizure-free outcome in PIH was reported to be 90% in a 9-year follow-up period[10], while the seizure free outcome in VPH was reported to be 74%[8], however, both authors stated that the underlying etiology may influence the success of the surgery. The remarkable outcome was reported in 75% of 12 patients treated with SA.[12] In this series, of the 10 patients

Engel Class I, 9 were operated with PIH approach while 1 underwent SA surgery. We also documented the only VPH in a 6-year-old girl with Sturge-Weber syndrome.

Acquired lesions such as porencephaly were known to have a better prognosis, along with Rasmussen's encephalitis and Sturge-Weber syndrome compared to neuronal migration defects like cortical malformation due to suspected involvement of the contralateral hemisphere.[8] Also, patients with cortical malformations tend to be operated at a younger age. Poor prognosis predictors include contralateral abnormality and abnormal hemispheres with extensive insular and subcortical heterotopic gray matter in imaging studies.[16-17] In this series, among patients with seizure freedom, 6 (60%) was diagnosed with porencephaly, 2 with hemispheric hemiatrophy, 1 with Rasmussen's encephalitis, and 1 with large MCA infarction.

Seizure frequency reduction may improve the quality of life of patients and cognitive capability. The delayed surgical procedure from the age of onset is associated with general outcomes, especially in verbal communication ability.[18] The average delay of surgery in our cases was 10.43±5.9 years (range 2 - 23 years), with an average onset of seizure started from 0 to 7 years old (mean 2.08±2.1 years).

Compared to anatomical and functional hemispherectomy, modified PIH had less risk of surgical complications and reoperation rate, although the seizure outcome did not significantly differ between techniques[6]. Hydrocephalus is a common sequel after hemispherectomy and is strongly correlated with anatomical hemispherectomy.[19] Transient postoperative hemiparesis or hemiplegia is also seen in most patients that underwent hemispherotomy; however, this phenomenon does not last in the long term.[18] In our series, five patients developed temporary worsening hemiparesis, which we promptly treated.

CONCLUSION

Hemispherotomy is a surgical procedure of hemispheric disconnection with good seizure-free outcomes to treat drug-resistant infantile hemispheric epilepsy and has a lower rate of postoperative complications compared to hemispherectomy. Our series is the most extensive

documentation of hemispherotomy in Indonesian population with Engel class I rate 62.5%, and 81.3% of patients showed improved symptoms.

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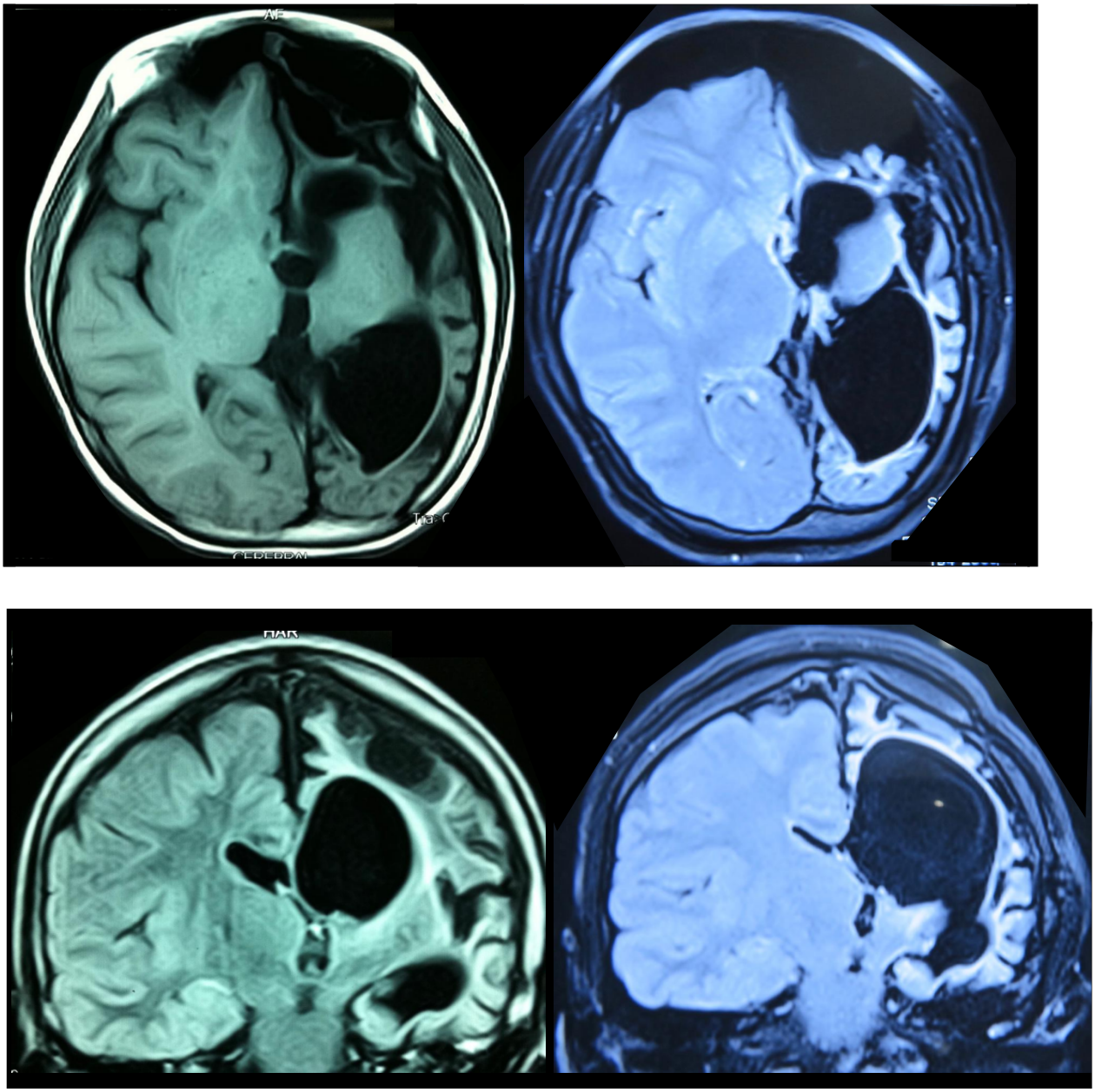

Figure 1. Preoperative (left) and postoperative (right) axial and coronal MRI slices of a 14 year-old female (Pt. no. 10) with right side infantile hemiparesis showed large porencephaly cysts in her left hemisphere. Left-sided hemispherotomy was performed (PIH). Postoperative observation resulted in complete seizure freedom (Engel class I) in 98 months.

No	Sex	Age at onset	Age at surgery	Seizure frequency (daily)	Clinical Semiology	Neuroimaging (MRI)	EEG	Surgical approach	Engel Outcome Score	FU length (M0)	Neuropsychological assessment	Complications
1	M	5	28	1-2	R infantile hemiplegia, focal to generalized tonic-clonic seizures	L hemispheric hemiatrophy	L hemispheric continuous slow, epileptiform backgorund	L, PIH	I	160	N/A	Worsening hemiplegia
2	M	6	12	N/A	R infantile hemiplegia	L hemispheric neonatal MCA infarction	L frontotemporal (ictal)	L, PIH	I	145	FIQ 50	
3	F	1	6	10-15	R infantile hemiplegia	L congenital porecenphalic cyst	Bilateral slow waves	L, SA	II	138	FIQ 82	
4	F	5	21	6-7	Focal to generalized tonic-clonic seizures	R severe atrophy	R temporal and frontal independently then generalization	R, SA	III	124	N/A	Worsening hemiplegia
5	F	1	11	4-5	R infantile hemiparesis	L hemispheric congenital porencephaly	L hemisphere (ictal)	L, PIH	I	119	N/A	
6	F	4	7	1-2	L infantile hemiparesis	R severe atrophy	L hemisphere	L, PIH	III	118	N/A	Worsening paresis
7	M	3	15	1-2	L infantile hemiparesis	R congenital porencephalic cyst	R frontocentral PLED	R, SA	I	117	FIQ 65	
8	F	1	6	N/A	L infantile hemiparesis	R Sturge-Weber syndrome	R slow activity, no epileptiform	R, VPH	N/A	N/A	FIQ 66	Worsening paresis
9	M	1	5	>10	Bilateral hemiplegia	Bilateral encephalomalacia, enlarged L ventricle, L mesial temporal sclerosis	Bilateral temporal epileptiform, low amplitude	L, PIH	II	99	N/A	
10	F	1	14	2-3	R infantile hemiparesis	L porencephalic cyst	L fronto-centro-temporal PLED, continuous slow	L, PIH	I	98	FIQ 64	
11	F	0.25	23	N/A	R infantile hemiparesis	L porencephalic cyst, damaged insula	L hemisphere continuous slow	L, PIH	I	88	IQ gr 5	
12	M	4	14	3-4	L infantile hemiparesis, focal to generalized tonic-clonic seizures	R hemispheric porencephaly	R frontal (ictal)	R, PIH	I	83	FIQ 99	
13	M	2	22	5	L infantile hemiparesis	R congenital porencephaly	R hemisphere slow waves	R, PIH	IV	76	IQ gr 5	
14	F	2	13	1-2	L hemiparesis, focal to generalized tonic-clonic seizures	R large porencephaly, large intracerebral hemorrhage	R continuous slow waves	R, PIH	I	54	FIQ 51	
15	M	5	18	0-1	R hemiparesis, focal to generalized tonic-clonic seizures	L hemispheric hemiatrophy	Biparietal spikes	L, PIH	I	53	FIQ 75 Wada test: no memory function at L hemisphere	Worsening hemiparesis
16	M	N/A	24	N/A	R infantile hemiparesis	L fronto-parieto-temporal porencephaly		L, PIH	N/A	N/A	N/A	
17	F	7	11	3-4 weekly	L infantile hemiparesis, focal to generalized tonic clonic seizures	R Rasmussen's encephalitis	R slow hemisphere	R, PIH	I	29	N/A	
18	F	3	12	3-5	R infantile hemiparesis	L hemispheric porencephaly	(ictal) L hemisphere, interictal epileptic discharges	L, SA	II	26	FIQ 59	
19	M	0.3	12	N/A	Hemispheric epilepsy	L congenital porencephaly	L continuous slow waves	L, PIH	N/A (reported	8	Cerebral palsy	

									seizure freedom after surgery)		
20	F	0	2	>20	R infantile hemiparesis	L polymicrogyria, cortical dysplasia	L temporocentral with diffuse electrophysiological disturbance	R, PIH	N/A (reported seizure freedom after surgery)	8	N/A
21	M	N/A	10	>20	L infantile hemiparesis	R hemimegalencephaly	R slow waves	R, PIH	N/A	5	N/A
22	M	N/A	14	N/A	R infantile hemiparesis	L hemispheric large encephalomalacia	N/A	L, PIH	N/A	5	N/A
23	F	1	9	N/A	L hemiparesis	R fronto-temporo-parietal porencephaly, encephalomalacia	(ictal) R hemisphere	R, PIH	N/A	3	FIQ 46
24	F	3	10	N/A	L infantile hemiparesis, focal to generalized tonic-clonic seizures	R Rasmussen's encephalitis	R occipital PLED, R epileptiform frontal, R temporal slow waves	R, PIH	N/A (reported seizure freedom after surgery)	1	FIQ 83

Table 1. Seizure Outcomes after Hemispherotomy

M=Male; F= Female; L=Left; R=Right; EEG: electroencephalography; N/A=Not Available; MCA=Medial cerebral artery; MTS= Mesial temporal sclerosis; MRI=Magnetic Resonance Imaging; PIH = Peri-insular hemispherotomy; SA = Shimizu approach; VPH = ventricular parasagittal hemispherotomy; FIQ = Full intelligence quotient; PLED = periodic lateralized epileptic discharges; FU = follow-up

Hemispherotomy for Intractable Hemiplegic Epilepsy in Indonesian Population

Muhamad Thohar Arifin[1], Zainal Muttaqin[1], Yuriz Bakhtiar[1], Erie Andar[1], Dody Priambada[1], Happy Brotoarianto[1], Ajid Risdianto[1], Krisna Prihastomo[1], Gunadi Kusnarto[1], Jacob Bunyamin[1]

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Conflict of Interest

All authors declare no conflict of interest.

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Author's Response To Reviewer Comments

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Dear Editor of Epilepsy & Behaviour Reports,We would like to thank the editor and reviewers for their comments, critics, and suggestions in improving this manuscript. Thank you very much. Best regards,Muhamad Thohar Arifin, MD, PhDDepartment of NeurosurgeryKariadi General Hospital/Faculty of Medicine Diponegoro UniversitySemarang, INDONESIA

-Reviewer 2 -Figure of a patient MRI showing one such case pre and post surgery (if possible one with each approach or at least one).This is overall a good study to show the center specific data on hemispherotomy of 18 patients. Written very well and to the point. Some minor revision are suggested1. If authors can add a MRI figure of a patient pre and post surgery, this will add to understanding of procedure. Since PIH is the most common procedure, to show one such example.We have provided the figure of a case operated with PIH. 2. Under Methods: Surgical procedure para3 last line- if can rewrite to mention: in a prior study this approach...(it is confusing with % and number if this is of your study vs prior)...We have edited the methods section.3. Results section- outcomes para line 4: replace on with in (4 patients). And line 5: if can explain temporary preserved symptom...We have deleted the sentence to avoid confusion. 4. Discussion para 2 line 10- replace from to "of the"... In our case, from 11 to - In our case, of the 11Sentence edited.(also following this para if authors can add 2-3 line mentioning why in their center seizure free outcome was lower compared to prior studies)We repeated the follow-up to the patients by phone calls, and the result of Engel Class I has been changed according to the latest follow up. 5. Discussion last para- line 5: change underwent to 'that underwent'Sentence edited.

-Reviewer 1 -This is a case series of 18 hemispherotomy patients from Indonesia, primarily reporting seizure outcomes. Several concerns also need to be addressed before this manuscript has any meaningful message for the epilepsy community:1.Authors should clarify how this series is different from other case series of hemispheric surgery reported from Asia including up to 129 patients (for example: Dagar et al. Pediatr Neurosurg. 2011;47(3):186-93.), other than just the country of origin.Our series reported only hemispherotomy case in Indonesia (24 from 723 cases), while we believe that the reported patients by Dagar et al., included all epilepsy cases. We believe that this report is useful to evaluate the outcome of epilepsy surgery in a developing country, especially in treating rarer cases. This information might complement the global data of epilepsy surgery report and thus might be useful in determining the strategy to improve the epilepsy surgery services in our country and region. 2.The methods section is severely lacking in details. What was their decision process for hemispheric surgery? How was seizure frequency ascertained? Was there a systematic evaluation for post-op complications? What were the MRI findings? Was there imaging evidence for normality of hemisphere contralateral to the one operated?We have included the imaging of one case who underwent hemispherotomy. The decision to proceed to hemispherotomy was determined by the consensus among epileptologist, epilepsy neurosurgeon, and neuropsychologist. 3.The variability in the time for measuring seizure outcomes is an important confounding factor. The primary outcome should be Engel class at 1 year follow up. Patients with <1 year follow up should be omitted. Engel outcomes for patients with longer follow up can be reported as secondary outcomes.For outcome result, we only included patients with follow-up duration longer than 12 months, although we listed all patients operated until July 2019. 4.The low proportion of class I outcomes seen in this study need to be explained. What was the role of patient selection criteria in driving outcomes?We repeated the follow-up to the patients by phone calls and the result of Engel Class I has been changed according to the latest follow-up. The result of Engel Class I outcome has been improved. 5.In the methods section, authors report measuring “motoric” outcome. What is this? How was it measured? I do not see it reported in the results.We decided to focus on the seizure frequency outcome, as it was impossible to assess the motoric outcome via indirect interview. 6.In the results section, authors mention that 1 patient developed “temporary preserved symptom”. What is this?We have revised the sentence to avoid confusion. 7.It may be desirable to remove the single patient with VPH, so that the series is more homogeneous.Our aim is to inform the international society that we have performed hemispherotomy in Indonesia. As there is no statistical evaluation in this study, we decided to include all patients with any approach, including VPH. 8.Methods, results, and discussion are all mixed up. For example, the patients characteristics described in methods section should be a part of results. In the subsection on surgical procedure, I do not think that the outcomes reported for SA (75% of 12 patients) is from authors work. This should be in discussion section. Similarly the discussion on indications of VPH should be moved to discussion section from methods.We have revised the methods, results, and discussion sections. 9.Introduction section: the distinction made by authors into “acquired” and “congenital” lesions is unclear.We have revised the sentence.

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Journal: Epilepsy & Behavior Reports

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Thank you for submitting your manuscript to Epilepsy & Behavior Reports. I have completed the review of your manuscript and a summary is appended below. The reviewers recommend reconsideration of your paper following major revision. I invite you to resubmit your manuscript after addressing all reviewer comments.

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I look forward to receiving your revised manuscript as soon as possible.

Kind regards,

Professor. Tatum
Editor-in-Chief
Epilepsy & Behavior Reports

Comments from the editors and reviewers:
-Editor

-
-Reviewer 1

-

This is a case series of 18 hemispherotomy patients from Indonesia, primarily reporting seizure outcomes. Several concerns also need to be addressed before this manuscript has any meaningful message for the epilepsy community:

1. Authors should clarify how this series is different from other case series of hemispheric surgery reported from Asia including up to 129 patients (for example: Dagar et al. Pediatr Neurosurg. 2011;47(3):186-93.), other than just the

country of origin.
2. The methods section is severely lacking in details. What was their decision process for hemispheric surgery? How was seizure frequency ascertained? Was there a systematic evaluation for post-op complications? What were the MRI findings? Was there imaging evidence for normality of hemisphere contralateral to the one operated?
3. The variability in the time for measuring seizure outcomes is an important confounding factor. The primary outcome should be Engel class at 1 year follow up. Patients with <1 year follow up should be omitted. Engel outcomes for patients with longer follow up can be reported as secondary outcomes.
4. The low proportion of class I outcomes seen in this study need to be explained. What was the role of patient selection criteria in driving outcomes?
5. In the methods section, authors report measuring “motoric” outcome. What is this? How was it measured? I do not see it reported in the results.
6. In the results section, authors mention that 1 patient developed “temporary preserved symptom”. What is this?
7. It may be desirable to remove the single patient with VPH, so that the series is more homogeneous.
8. Methods, results, and discussion are all mixed up. For example, the patients characteristics described in methods section should be a part of results. In the subsection on surgical procedure, I do not think that the outcomes reported for SA (75% of 12 patients) is from authors work. This should be in discussion section. Similarly the discussion on indications of VPH should be moved to discussion section from methods.
9. Introduction section: the distinction made by authors into “acquired” and “congenital” lesions is unclear.

-Reviewer 2

-

Figure of a patient MRI showing one such case pre and post surgery (if possible one with each approach or at least one).

This is overall a good study to show the center specific data on hemispherotomy of 18 patients. Written very well and to the point. Some minor revision are suggested

1. If authors can add a MRI figure of a patient pre and post surgery, this will add to understanding of procedure. Since PIH is the most common procedure, to show one such example.

2. Under Methods: Surgical procedure para3 last line- if can rewrite to mention: in a prior study this approach...(it is confusing with % and number if this is of your study vs prior)...

3. Results section- outcomes para line 4: replace on with in (4 patients). And line 5: if can explain temporary preserved symptom...

4. Discussion para 2 line 10- replace from to "of the"... In our case, from 11 to - In our case, of the 11

(also following this para if authors can add 2-3 line mentioning why in their center seizure free outcome was lower compared to prior studies)

5. Discussion last para- line 5: change underwent to 'that underwent'

Editor-in-Chief

Please ensure English and references are carefully reviewed for correctness.

Use "drug-resistant" for intractable/refractory/pharmaco-resistant; "anti-seizure drug" for antiepileptic drug.

Mail FK UNDIP

MUHAMAD THOHAR ARIFIN <thohar@fk.undip.ac.id>

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Journal title: Epilepsy & Behavior Reports
Article Number: 100337
Corresponding author: Dr. Muhamad Thohar Arifin
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