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From: MUHAMAD THOHAR ARIFIN thohar@fk.undip.ac.id 
Subject: Bali Med J Submission
Date: 02 July 2020 . 6 .43
To: Editor Bali Medical Journal editorbalimedicaljournal@gmail.com

Dear Chief Editor BMJ,

Enclosed is our manuscript entitled "Awake craniotomy procedure for near eloquent cortical area for brain tumour case series: initial experience and the anaesthetic challenges"

We believe that this report and the published data we reviewed would be of interest to readers of Bali Medical Journal and hope that our manuscript will receive favorable consideration for publication.

Thank You
Muhamad Thohar Arifin



Awake
Craniot...al.docx



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

Bali Med J Submission ID-1916

2 pesan

Editor Bali Medical Journal <editorbalimedicaljournal@gmail.com>
Kepada: thohar@fk.undip.ac.id

24 Juli 2020 19.49

Dear M Thohar Arifin

Thank you for submitting your precious work entitled "**Awake craniotomy procedure for near eloquent cortical area for brain tumour case series: initial experience and the anaesthetic challenges**"

As per our reviewer suggestion, **we have spot some point for manuscript improvement.**

1. Please fill the conflict of interest form that we sent in the attachment below
2. Mention any limitation of the study, since current study only a case series.
3. Regarding the figure 3, there are some untranslated word and unknown abbreviation (lesi, S, M, please add figure complete abbreviation).
4. Please try to use grammar check software for vocabulary (e.g smokey, ginger, grammarly) enhancement and reduce any kind of mistyping.

Looking forward to hear form you soon

Best and regards

Managing editor Bali Medical Journal

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Kepada: Editor Bali Medical Journal <editorbalimedicaljournal@gmail.com>

27 Juli 2020 13.43

Dear Chief Editor BMJ,

Thank you for your email.

Bellow are my respond

Editor comment :1. Please fill the conflict of interest form that we sent in the attachment below

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Editor comment : 2. Mention any limitation of the study, since current study only a case series.

Author respond: Thank you for your comment, the limitation of this study was added

Editor comment : 3. Regarding the figure 3, there are some untranslated word and unknown abbreviation (lesi, S, M, please add figure complete abbreviation).

Author respond: Thank you for your comment, the translation was done.

Editor comment : 4. Please try to use grammar check software for vocabulary (e.g smokey, ginger, grammarly) enhancement and reduce any kind of mistyping.

Author respond: Thank you for your comment, grammar error was checked and corrected.

Thank You

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On 24 Jul 2020, at 19.49, Editor Bali Medical Journal <editorbalimedicaljournal@gmail.com> wrote:

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2 lampiran



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1 **Awake Craniotomy Procedure for Near Eloquent Cortical Area for Brain Tumour**
2 **case series: Initial Experience and the Anaesthetic Challenges**

3
4

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32

33 **Abstract**

34 *Introduction*

35 The main objective of the surgical procedure is to achieve maximum resections with minimal
36 functional neurological deficits for the patient with intrinsic tumours near the eloquent cortical

37 area. The awake craniotomy procedure is currently the key option for achieving optimum safe
38 resection. We report our two years of experience in establishing an awake craniotomy in the
39 Kariadi General Hospital, evaluating the adoption of the technique and the outcome of the
40 surgery.

41 *Methods*

42 This is retrospective study analyzed data from all patients medical record, who were performed
43 an awake craniotomy
44 from January 2018 to January 2020 at the Dr Kariadi General Hospital/Diponegoro University.
45 The specific anaesthesia technique designated for this procedure was adopted. Sonography
46 was introduced to determine the border of the tumour before and after surgery. Phase reversal
47 using cortical grid was used to recognize the central sulcus, motor and sensory cortex. Cortical
48 stimulation using a monopolar stimulator was used to recognize the eloquent region
49 surrounding the tumour. Enbloc resection was done with a fully conscious patient as well as
50 with careful neurological testing during surgery.

51 *Result*

52 The pre-operative Karnofsky Performance Status (KPS) mean was 63, with remarkable
53 improvement to 70. The length of surgery was varying from 120 to 420 minutes with mean
54 was 270 min. Our procedure was done for tumours situated in the Broca area in 3 cases, motor
55 gyrus in 7 cases and premotor gyrus in 3 cases. None of the patient needed intensive post-
56 operative care. Pathological findings show glioma in 9 patients, metastases in 3 patients and
57 tuberculoma in 1 patient.

58 *Conclusion*

59 [Based on our experience](#), Awake craniotomy is a technique designed to preserve
60 eloquent cortex and improving our knowledge of the functional structure of brain centres.
61 Together with the neurosurgeon, neurophysiologist, neuroanaesthesia and OR nurse team,
62 these advanced neurosurgery procedures can be performed without hesitation in developing
63 countries.

64

65 Key Word : awake craniotomy, eloquent cortex, functional brain centres

66

67

68 **Introduction**

69 Surgical procedure for intrinsic tumours near the eloquent cortical area aims to obtain
70 maximum resection with minimal functional neurological deficits for the patient. To obtain
71 maximal safe resection in the eloquent area of the brain, the awake craniotomy procedure is
72 currently the main choice.¹ Awake craniotomy has become more commonly used worldwide,

73 but it is still new in our country. This approach is one of entity of safe neurosurgical procedure
74 for the lesion on the eloquent area. As a considered advance neurosurgical procedure, it
75 requires rather complicated pre-operative as well as intra-operative preparation.²

76 Intraoperative cortical stimulation has been used by Foerster since 1930 and then later
77 by Penfield and colleagues.³ Recently intraoperative cortical stimulation has been adopted to
78 the identified eloquent cortical area in the brain. Cortex area of the brain will evoke a certain
79 response during stimulation.³ Currently, awake craniotomy and intraoperative monitoring
80 were used as standard procedure for the near eloquent cortical area to achieve maximal safe
81 resection.^{1,2,5} Many neurosurgical centres with limited resource have been practising this
82 complex neurosurgical procedure.

83 We are retrospectively reporting our two years' experience of establishing awake
84 craniotomy procedure in Kariadi General Hospital evaluating the adopting technique and
85 surgery outcome.

86

87 **Method**

88 **Patient selection**

89 This study involved an analysis of data from all patients medical record, who were
90 performed awake craniotomy from January 2018 to January 2020 at the Department of
91 Neurosurgery Dr Kariadi General Hospital / Diponegoro University. Starting in 2018, Dr
92 Kariadi General Hospital Medical Centre launched its first intraoperative monitoring unit to
93 develop more advanced and safe neurosurgery procedures. Patients who performed the
94 procedure were patients with tumours near the eloquent area of the brain based on pre-
95 operative MRI. We define the eloquent cortex is speech area on the dominant hemisphere and
96 motor area on both hemispheres.

97 The speech function in patients which the tumour nearby the Broca area was analyzed by
98 neurophysiologists by examining the names of objects, remembering, counting, fluency in the
99 language, reading and writing before and intraoperatively. Currently, awake craniotomy
100 procedure is accompanied by brain mapping of the eloquent cortex become the gold standard
101 procedure to increase the maximal functional of resection.

102 Our surgery procedure was performed to achieve maximal brain tumour removal with minimal
103 risk of permanent post operative neurological deficits.⁵ In advanced neurosurgery centres,
104 intraoperative MRI is complementary to this procedure. Intraoperative sonography was
105 routinely used in our centre due to lack of intraoperative MRI. Intraoperative sonography
106 (General Electric) was used routinely to achieve the maximally resection.⁶

107 **Cortical and Subcortical Stimulation**

108 Before tumour resection is performed, the patient is woken up, and then the
109 neurophysiologist and neurosurgeon will communicate with the patient. Patients are asked to
110 perform tasks verbally and visually to analyze the ability to speak during stimulation. The
111 existence of dysnomia interrupted speech or difficult speech will be noted.

112 **Continuous Monitoring of Transcortical MEPs by Direct Cortical Stimulation**

113 Transcortical monitoring was performed to detect compound muscle action potentials
114 (CMAPs), several muscles on the contralateral side of the lesion was monitored using 27-
115 gauge bipolar subdermal needle electrodes. We monitor abductor pollicis brevis muscle and
116 deltoid muscle for upper extremity, quadriceps femoris muscle, anterior tibialis muscle and
117 gastrocnemius or lower extremity. Cortical stimulation was performed every 8-10 mm with
118 repetitive biphasic square-wave alternating polarity currents (pulse width, 0.2 msec;
119 frequency, 50 Hz; duration, 1–2 seconds). To detect seizure and after-discharge, we monitored
120 with continuous digital electrocorticogram.^{4,7} Cortical stimulus starts from 2 mA and steadily
121 increased 1mA until electrocorticogram abnormality was noted (maximum stimulus intensity
122 was six mA (biphasic current; 12 mA). The duration of the stimulus on the brain surface is 2
123 seconds each time. Generally, 4-6 mA was the maximal stimulus for speech area and ten mA
124 for the motor area.

125 In patients with identified speech areas, a safe resection limit is 1-2 cm from the talking
126 area. In the motoric area, the resection limit that has been identified is closer to 0.5 cm.
127 Resection is stopped when there is total speech disturbance but can be continued if within 5
128 minutes language skills improve.

129 **Anesthesia Procedure**

130 All patients were then treated with 0.25% Bupivakain and 5 µg / ml of adrenaline in a scalp
131 block mixture. Subcutaneous administration was performed at six sites on either side of the
132 scalp. The participating nerves included the super-orbital nerve, the supratrochlear nerve, the
133 auriculo-temporal nerve, the zygomaticotemporal nerve, the occipital nerve (larger) and the
134 occipital nerve (lesser).^{8,9}

135 All patients were subject to blockage at all six sites of scalp nerves. Oxygen at 3 l / min was
136 initially supplied by nasal prongs, Dexmedetomidine infusion as initiated sedation started
137 before the scalp block procedure at a dose of 1.0 µg / kg for 20 minutes (loading dose) followed
138 by 0.2-0.7 µg / kg / h (maintenance dose). Fentanyl in small dose (25 µgr – 50 µgr) bolus, was
139 prepared when the patient response to pain stimuli. Target Controlled Infusion (TCI) propofol
140 was prepared as backup sedation in all cases where the patient was restless and agitated.⁸

141 The goal of the sedation was to obtain an OAAS of 2 (response only after moderate prodding
142 or shaking) of 3 (responds only after a name is spoken loudly, or repeatedly, or both) for scalp
143 blocks. Throughout the block, blood pressure (BP), heart rate (HR) and oxygen saturation

144 were stable. Dexmedetomidine was maintained during cortical mapping and stimulation at the
145 lowest dose (0.2-0.4 µg / kg / h). Speech, sensory and motor cortical areas have been mapped
146 by cortical electrical stimulation and evaluated by EMG and clinical response.
147 Communication with the patient was maintained throughout the assessment. All patients were
148 comfortable during surgery without any worsening of their neurological deficits. All tumours
149 were successfully removed while patients were in an arousable and cooperative state. All
150 haemodynamics parameters were stable throughout the operation. During the closing stage,
151 the sedation deepened again.⁹

152 **Surgery procedure**

153 The patient's head was positioned using a Mayfield headframe with a suitable position, mainly
154 supine with a slight bending. (Figure 1) Skin incisions are made in a number of ways
155 determined by the location of the tumour followed by craniotomy and dural opening, and we
156 identify the Rolandic portion then a 6-contact titanium electrode strip is placed. (Figure 2).
157 The median nerve then stimulated, identifying the central sulcus and precentral gyrus with
158 somatosensory evoked potential (SSEP) phase reversal. The functional mapping of the motor
159 cortex is then performed using the Caldwell© stimulator. Identification of eloquent cortical
160 area was made, then strip electrode and the margin of the tumour were placed. We adjust the
161 strip electrode to achieve maximal CMAPs of the target muscles with a threshold of 30 mA or
162 less.

163 A strip electrode is used to track the continuous MEP (stimulation train, 5; frequency, 500 Hz;
164 pulse length, 0.5 msec) during tumour removal using a neurophysiological monitoring system
165 (Caldwell). During tumour removal, we monitor the motor trajectory through the resection
166 cavity with subcortical stimulation.⁶ Each eloquent cortical area was stimulated at least two
167 times.

168 Our surgical procedures are carried out to achieve maximum removal of brain tumours with a
169 minimum risk of permanent neurological deficits after surgery. Intraoperative sonography
170 (General Electric) is used routinely to get the maximal resection. Maximum brain removal was
171 defined by visualization of T1-weighted contrast-enhanced MRI for tumours with a ring
172 enhancement suspected to be grade IV gliomas and elimination of the region identified by
173 signal hyperintensity of T2-weighted MRI for non- or partially contrast-enhanced tumours
174 suspected to be grade I, II or III gliomas. Histopathological diagnosis of tumours was based
175 on the previous criteria of WHO in 2007.¹⁰

176 **Intraoperative electrostimulation technique**

177 By the time of electrostimulation of the brain aimed at direct identification of cortical speech
178 centres, the patient must be awakened out of anaesthetic sleep. Further, stable verbal and
179 psycho-emotional contact should be established with the patient.¹¹ Cortical area remote from

180 tentative Broca's and Wernicke's area should be selected to adjust electrostimulation current.
181 After current adjustment, the mapping itself should be carried out. The entire opened surface
182 of the cerebral cortex should be consistently studied starting from the supposedly "silent"
183 regions to the functional areas. When detecting errors in test execution during intraoperative
184 neuropsychological testing, the procedure should be paused, and then stimulation should be
185 repeated 1—2 times in the area identified as a cortical speech centre. Cortical speech areas
186 identified using direct electrical stimulation should be marked with sterile paper (cellulose)
187 labels with numbers. Seizure activity of the cerebral cortex should be monitored during the
188 entire electrical stimulation procedure. In the case of readiness for convulsions, electrical
189 stimulation of the brain is stopped, and surgical wound is irrigated with prefabricated cooled
190 saline solution, and intravenous anticonvulsants are administered, if necessary: sodium
191 valproate or levetiracetam. Electrical stimulation of motor areas of the cortex is carried out
192 either during the search for cortical speech areas, or, additionally, cortical motor centres in the
193 case of anatomical spread of space-occupying lesions in the direction of the motor cerebral
194 convolutions.¹² The areas of the motor cortex are also labelled with numbered cellulose piece.
195 (Figure 3.)

196 **Ethical clearance**

197 This research was approved by the institution review board of Kariadi General
198 Hospital, in accordance with the Helsinki declaration. Prior written informed consent was
199 obtained from all patients. For patients under the age of 18 years, informed consent obtained
200 from a parent and/or legal guardian.

201

202 **Result**

203 We already performed awake craniotomy in 13 patients from January 2018 to January
204 2020 at Kariadi General Hospital Semarang. In our centre included ten male patient and three
205 females, with a range of age between 29 - 60 years old. In all cases, diagnosis pre operative
206 was done based on multimodal 1,5 Tesla MRI, which included pre- and post contrast T1-
207 weighted, T2-weighted and fluid-attenuated inversion recovery images (FLAIR). Pre-surgical
208 consideration was made on eloquent brain area.

209 Awake craniotomy procedure was performed on the left side in 911 cases and on the
210 right side in 2 cases. The awake craniotomy procedure in this study was 50 per cent for the
211 eloquent motor cortex (7 cases), 3 cases for the Broca area and 3 cases for the premotor gyrus.
212 The median length of surgery for the waking craniotomy procedure was 270 minutes, with a
213 range between 120 and 420 minutes. (Table 1.)

214 Awake craniotomy improved the Karnofsky Performance Score, the mean pre-
215 operative KPS was 63 ± 5 , and the post-operative KPS was 70 ± 6 . The findings of the

216 histopathological analysis included 3 cases of high-grade glioma, 6 cases of low-grade glioma,
217 three patients with metastatic tumour and one patient with tuberculoma. In this study, one
218 patient who died five days after surgery was reported according to the above data. (Table1.)
219

220 **Discussion**

221 The anaesthetic management objectives of awake craniotomy are to facilitate patient
222 cooperation, maintain general homeostasis and reduce interference between anaesthetic agents
223 and the quality of the electrophysiological recording.¹² It creates unique sedation that acts in
224 subcortical regions similar to natural sleep without respiratory depression. This does not
225 interfere with electrophysiological monitoring and thus enables brain imaging during awake
226 craniotomy.^{9,13}

227 Evoked potential technique aimed at somatosensory and motor mapping is widely used
228 in the past decade. However, the reliability of this method with respect to the localization of
229 Rolandic fissure is not optimal; the accuracy of this method is 91 to 94%. In addition, the
230 phase reversal procedure makes the position of the Rolandic fissure easier to find and does not
231 provide details on the distribution of motor functions in the surrounding areas under surgery.
232 The total sensitivities and adverse effects are calculated at about 96% and 79% respectively.¹⁴
233 Although the motor evoked potential technique has been improved, it enables evoked potential
234 recording only in monitored muscles but does not allow detection and prevention of possible
235 deficit in the muscles not subject to monitoring. Monitoring of motor evoked potentials does
236 not include the assessment of complex movements and voluntary movements, which are the
237 ultimate goal of the patient's physical activity. A further limitation of this method is that it
238 cannot be used to monitor speech functions, memory, and other higher brain functions, which
239 are of key importance for patient's quality of life.¹⁵

240 After bone removal, sonography was used to identify the location and the border of the
241 tumour to determine the appropriate incision for dura mater. After dura mater opening, strip
242 electrode for direct corticography is placed. Participation of neurophysiologist,
243 neuroanaesthetist and neurosurgeon is key for this procedure. Direct identification of cortical
244 speech area, motoric or sensory area was done using electrostimulation.¹⁵ Intraoperative
245 electrostimulation mapping provides pre-operative real-time detection of the location of
246 functional areas and facilitates the choice of the best surgical approach of tumour resection
247 within these areas. Another important task is mapping of the subcortical structures along with
248 an examination of the cortex prior to resection. Brain damage studies suggest that damage to
249 the pathways is followed by the development of more severe neurological deficits than in the
250 case of cortex injury.¹⁵

251 Enforced supporting equipment included the intraoperative monitoring unit, the
252 headframe and the rest were the standard neurosurgery OR instruments.

253

254 **Limitations of this study**

255 Methodological rigour and the meticulous performance of the direct electrical
256 stimulation procedure are required to avoid any false positive or false negative results, which
257 could lead to inadequate tumour resection or cause permanent neurological deficits. If all the
258 technical rules are not respected faithfully, inaccurate results will create a false sense of
259 security, which could lead to undesired surgical results and permanent neurological sequelae.

260 Another limitation, this report is retrospective, no randomization to select the case and
261 does not have a control arm.

262

263 **Conclusion**

264 Anatomical consideration and pre-operative data (neuroimaging, intraoperative
265 electrophysiological and neuropsychological monitoring), as well as strategies for active
266 surgical intervention, are presented. Awake craniotomy is a technique designed to preserve
267 speech and motor functions and improving our knowledge of the functional structure of brain
268 speech centres, memory, counting, writing, hearing and visual perception and other higher
269 neurological functions.

270

271 **Funding**

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274 Inovasi Nasional No 225-57/UN7.6.1/PP/2020.

Glossary

Table 1. Characteristic data

Characteristic	No.
Median age in years (range)	46 (29 – 60)
Sex (%)	
Male	10 (77)
Female	3 (23)
Karnofsky Performance Scale (KPS)	
Pre op (Mean ± SD)	63 ± 5
Post op (Mean ± SD)	70 ± 6
Length of surgery	
Range (minutes)	120 - 420
Mean (minutes)	270
Relationship w/ eloquent brain areas (%)	
Broca area	3 (23)
Motor gyrus	7 (53)
Premotor gyrus	3 (23)
Pathology (%)	
Glioblastoma multiforme	1 (7,6)
High-grade glioma	2 (15,3)
Low grade glioma	6 (46)
Metastasis	3 (23)
Tuberculoma	1 (7,6)
Side of the lesion (%)	
Left	11 (84)
Right	2 (15)

Deleted: mean

Deleted: mean



Figure 1. Positioning for surgery using headframe Mayfield®

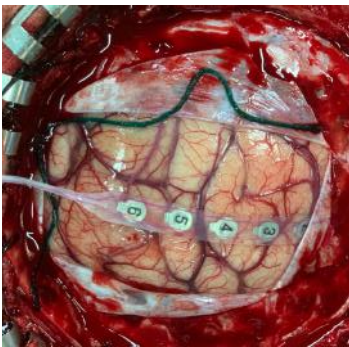


Figure 2. Cortical grid mapping

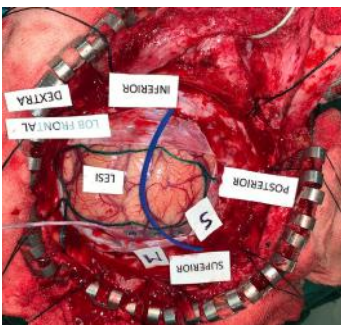


Figure 3. Surgeon view for tumour located on right frontal lobe (abbreviation S= Sensoric gyrus, M= Motoric Gyrus, Lesi = lesion)

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Editor Bali Medical Journal <editorbalimedicaljournal@gmail.com>

27 Juli 2020 23.12

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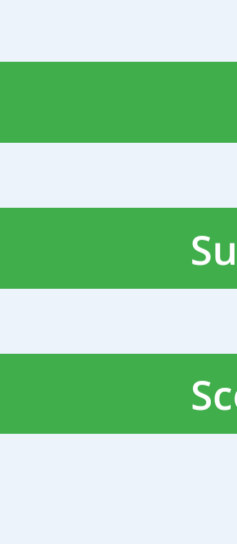
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