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Gamma Knife Radiosurgery for Tremor Movement Disorder: A Systematic Review

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Abstract

AIM: The goal of this systematic review is to know how outcome of GKRS for tremor movement disorder.

METHODS: Literature searching was conducted in database online that is PubMed, Science Direct, Cochrane Library, Google Scholar and hand searching with keyword “gamma knife,” “parkinson,” “tremor,” “success rate,” “good outcome,” and “free tremor.” Articles included were full-text and observational study and written in Bahasa or English.

RESULTS: This systematic review used only six articles, which five of them examined ET and the other PD. Majority of studies used Fahn-Tolosa-Marin clinical tremor rating scale (TRS) for evaluation pre- and post-GKRS. However, the duration of follow-up is varies from <1 year until 76 months. The doses are also varies from 110 until 150 Gy (Median 120–130 Gy). A study report that 1 year after GKRS, ET patients could have 58% improvement in writing and 51% in drawing. Other study, which of median follow-up was 36 months, had 69% of samples showed improvement in both action tremor and writing scores. Ohye *et al*. in 2008 reported that since 1992, they have 80% successful in GK thalamotomy for tremor, either ET or PD. Similar author has been done multivariate study in six Japanese institution which of result was GKRS thalamotomy could be alternative treatment for intractable tremor, either ET or PD until 24 months. All of the study about ET have improvement results with GKRS in ventralis intermedius (VIM) of the thalamus. However, one study about PD evaluated GKRS in subthalamic nucleus (STN) of thalamus and got neurological complication with higher-risk of GKRS hyper response.

CONCLUSION: GKRS, especially VIM thalamotomy, offers effective and safe alternative for ET and PD. We need more studies with approved method to answer this clinical question accurately. However, the study comparing GKRS and open surgical is still needed.

Introduction

Tremor is movement disorder that can impair the quality of life. Moreover, the most common type of tremor in population are essential tremor (ET) and Parkinson’s disease (PD). The prevalence of ET is almost 300–400 cases/100,000 population or 0.3 until 5.6% in general population [1]. In the United States, there are more than 5 million people who affected ET. For PD in 2016, Global’s prevalence of PD was more than 6 million where Indonesia had 146,236 people with PD (21.7% change in age-standardized rate, from 1990 until 2016) [2]. These number will be increased because geriatric population also greater each year.

Many tremor patients become unresponsive to the medication or suffer side effects from medication. Because of these limitations, surgical intervention is needed. Some patients are poor candidate for surgery because older age, using anticoagulant, presence of coagulopathy, and presence of serious medical. Those patients, who cannot undergo open surgery, choose gamma knife radiosurgery (GKRS) for alternative intervention [3]. This systematic review aims to know how effectivity of GKRS for ET and PD.

Methods

Literature searching was conducted on June 13, 2020 in database online, that is PubMed, Science Direct, Cochrane Library, Google Scholar, and hand searching with keyword “gamma knife,” “Parkinson,” “tremor,” “success rate,” “good outcome,” and “free tremor” along with its synonyms and related terms (Table 1 and Figure 1). Searching strategy also used hand searching and found two articles.

In this report, only published meta-analysis, systematic reviews of clinical trials (randomized and control trials (RCTs), systematic reviews of observational studies (case control or cohort), RCTs, and observational studies were included in the study. The chosen articles were published within 15 years and written in English or Indonesian. After literature

Table 1: Searching strategy

Database	Key Words	Hits	Selected article
PubMed	"gamma knife" AND ("Parkinson"" OR "tremor") AND ("success rate" OR "good outcome" OR "free tremor")	7	3
Cochrane	"gamma knife" AND ("Parkinson" OR "tremor"") AND ("success rate" OR "good outcome" OR "free tremor")	0	0
Science Direct	"gamma knife" AND ("Parkinson" OR "tremor") AND ("success rate" OR "good outcome" OR "free tremor")	133	0
Google Scholar	"gamma knife" AND ("Parkinson" OR "tremor") AND ("success rate" OR "good outcome"" OR "free tremor")	766	4

selection, a critical appraisal was performed using Guidelines for Therapeutical Study based on Center of Evidence-Based Medicine, University of Oxford. Appraisal and review were done by two authors. If there were different decision about article, the other author make final decision.

Results

This systematic review used only eight articles which six articles from database and other from hand searching. There are six articles which examined effectivity of ET and only one article examined PD. We appraised six articles which as shown in Table 2.

The summary of each article is shown in Table 3.

Majority of studies used Fahn-Tolosa-Marin clinical tremor rating scale (TRS) for evaluation pre- and post-GKRS. However, the duration of follow-up varies from < 1 year until 76 months. The doses are also varies from 110 until 150 Gy (Median 120–130 Gy).

The study was held by Kondziolka *et al*. examined 31 patients who underwent GKRS for refractory ET. They used Model U, B, and C Leksell Gamma Knife with maximum dose 130–140 Gy. Only 26 patients evaluated because five patients were lost to follow-up. Pre-operative TRS score was 3.7 ± 0.1 with after GKRS was 1.7 ± 0.3 ($p < 0.001$). For handwriting, pre-GKRS score was 2.8 ± 0.2 and post-GKRS was 1.7 ± 0.2 ($p < 0.001$). The median follow-up was 36 months [5].

Young RF in 2010 report that mean of pre-operative TRS for drawing was 3.3 ± 0.8, and the mean of post-operative was 1.6 ± 1.4, which means 51% improvement. Moreover, for writing score, there is an improvement from 3.1 ± 1.3 to 1.3 ± 1.2 (58% improvement) ($p < 0,001$). This number was got from follow-up 56 ± 31 months. This study also divided samples to two groups, unilateral procedure (119 patients) and bilateral procedure (42 patients). The result of both groups was similar with overall result that drawing and writing score improved [6].

A multicenter study in Japan by Ohye *et al*. in 2012 reported 72 patients underwent GKRS for ET or PD. However, in last follow-up (24 months), only 73.6% who completed follow-up. This study used different protocol for examination, Unified Parkinson's Disease Rating Scale (UPDRS). UPDRS has four parts, those are Part I about mentation, behavior, and mood, Part II about activities of daily living, Part III about motor examination, and Part IV about complications. The tremor score changed significantly in both types of tremor (PD: $p < 0.001$, ET: $p = 0.022$). Tremor severity at 24 months after GKRS was reduced ($p < 0.001$ for PD, $p = 0.039$ for ET). In PD patients, clinical improvement in symptoms became apparent approximately 3 months post-GKRS [11].

Niranjan *et al*. (2016) reported 20 years' experience in GKRS for ET in median dose 140 Gy (130–150 Gy). Mean TRS improved from 3.19 ± 0.74 before to 1.23 ± 1.01 ($p < 0.001$). This improvement included three parts of TRS. For long-term follow-up (more than 3 years) was avail-able in 28 patients. The mean of TRS improved from 3.1 to 1.0 ($p < 0.001$). That means that 42.85% had excellent outcome (TRS of 1), and 28.57% had good outcome (tremor score of 2) post-GKRS [10].

Cho KR report seven patients who underwent GKRS for tremor in maximal dose 130 Gy. Only 50% of ET patients who had improvement in 4-month follow-up. Improvement in the total TRS score ($p = 0.043$) and tremor score ($p = 0.041$) was found to be significant. However, the writing and drinking scores did not statistically significance (p value for writing = 0.059, p value for drinking = 0.189) [9].

The last and one only study about effectivity GKRS in only PD patient (Drummond *et al*.). They only report five patients with UPDRS and neuropsychiatry examination for outcome of GKRS with maximum doses 110–120 Gy. Three patients who were evaluated at 12 months post-GK had an improvement in mean UPDRS- III scores for rigidity, tremor, and bradykinesia. The UPDRS-III pre-GKRS score of 41.0 improved by an average of 41.5% after GKRS. There was no significant change in psychiatry examination (MMSE, PDQ-39, or BDI) at 12 months [3].

Table 2: Critical appraisal

Article	Years of publication	Validity					
		Randomization	Similarity of the groups	Similarity of treatment between the groups	Diagnostic test was used	Intention to treat	Blinding
Duma M	1998	−	−	−	+	+	−
Kondziolka D	2008	−	−	+	+	+	?
Young RF	2010	−	?	−	+	+	?
Lim SY	2010	−	−	+	+	+	+
Ohye C	2011	−	+	+	+	+	+
Cho KR	2015	−	+	+	+	+	−
Niranjan A	2016	−	+	+	+	+	−
Drummond PS	2019	−	+	+	+	+	−

+: Yes, −: No, ?: Unclear.

Table 3: The summary of articles

Article	Years of publication	Design study	Subject/population
Duma *et al*. [4]	1998	Observational Study	There were 34 patients with disabling tumor due to PD who underwet GKRS from March 1991 to December 1996
Kondziolka *et al*. [5]	2008	Observational Study	Samples are 31 patients who underwent GKRS for refractory ET from December 1996 to July 2005
Young *et al*. [6]	2010	Observational study	Between February 1994 and March 2007, 172 patients underwent unilateral (130) or bilateral staged (42) VIM thalamotomy procedures with the Model U or Model C Leksell GK unit. GKRS was performed by senior author
Lim *et al*. [7]	2010	Observational study	This study uses 18 patients (15 with ET, 3 with PD tremor) underwent GKT for ET or PD tremor at the Toronto Western Hospital from September 1, 2006, to November 30, 2008
Ohye *et al*. [8]	2011	Observational study	There are 72 patients with refractory tremor of PD or ET from six institutions in Japan with 24-month follow-up
Cho *et al*. [9]	2015	Observational study	Seven patients underwent GKT (five males and two females). Six patients were diagnosed with ET, and one patient was diagnosed with PD in whom tremor was the predominant and disabling symptom
Niranjan *et al*. [10]	2016	Observational study	There are 73 qualified ET patients were treated with GKRS between August 1996 until December 2015
Drummond *et al*. [3]	2019	Observational study	Four patients PD was medication-refractory tremors, with three also experiencing disabling dyskinesias

ET: Essential tremor, PD: Parkinson's disease, GKRS: Gamma knife radiosurgery, VIM: Ventralis intermedius.

Discussion

Patients who fail in medical treatment have another management options include deep brain stimulation (DBS) or GKRS. The DBS has been used for the treatment of tremor since its introduction in 1980s due to advantages over other surgical treatments such as reversibility, individual modifiability, and non-destructive nature. For certain patients, including the elderly, taking anticoagulants or with coagulopathy, and/or those with medical comorbidities, DBS as invasive procedures may present unacceptable risks [9]. This discussion of this systematic review is divide into four parts, those are effectivity, complication, anatomical region, and dose of GKRS.

Effectivity of GKRS in tremor movement disorder

All of the study used in this systematic review did not compare GKRS versus DBS, as gold standard treatment, for tremor treatment because GKRS patients have no good condition for DBS surgery. Patient with geriatric age, long-term use of anticoagulants, or other serious medical conditions cannot be candidate for DBS. Hence, effectivity of GKRS was not compared with other treatment.

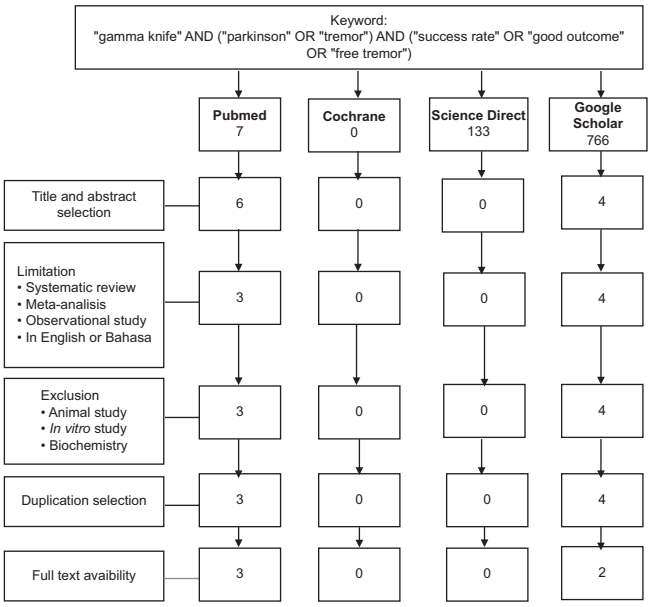

Figure 1: Literature searching

Majority studies had good outcome in GKRS for tremor disease. Young and Kondziolka use drawing and writing score of Fahn's tools (FTM score) for follow-up. Up to 69−81% of patients with essential tremor showed improvements in drawing and 77% in writing scores in 12-month follow up. However, they did not score head tremor, many patients with neck, jaw, or head tremor had improvement of that symptom [5], [6]. A cohort study reported that 92.3% initial tremor relief and 88.2% maintained long-term tremor relief. GKRS resulted in statistically significant improvements in all FTM scores (tremor, handwriting, drawing, and drinking) [10]. The other study from Ohye (2012) used UPDRS and get tremor severity at 24 months after GKRS was reduced [8]. A study by Cho had more detail that improvement of tremor can be seen in 4 months after GKRS [9]. However, there was patient in Kondziolka's study with good outcome in 1-month follow-up [5].

Niranjan also concluded that there are three main benefits of GKT. First, GKT can be used for patient with high risk of morbidity and possible mortality from surgical procedures [12]. Second, GKT has less cost than DBS with similar results [6]. Moreover, the last benefit is that GKT provides radiation that extends beyond the 50% isodose line, with a positive effect on the kinesthetic cells within the thalamus [13]. However, there are still no studies about effectivity of GKT compare to DBS or other surgical option for tremor.

In this systematic review, we found that all of selected studies showed that GKRS can be alternative treatment for essential tremor and Parkinson's Disease. Although we only used six studies, all of studies showed the good outcome of GKRS in tremor. Those good outcomes were got in minimum 1-month follow up. The other studies which compare both methods and in similar group are needed. If effectivity almost similar and complication, which discussed in next section, lower in GKRS, the gold standard treatment will be changed to GKRS.

Complication of GKRS in tremor movement disorder

Certainly GKT is attended by infrequent; however, sometimes serious complications caused

by individual and unpredictable excessive radiation reactions. There is a study which reported eight patients who had sustained serious complications involving radiosurgical lesioning procedures with GKRS for the treatment of movement disorders [11]. However, the overall range of patients who had undergone lesioning procedures at the establishment in question was unknown, and thus, it had been not possible to calculate the particular incidence of such complications.

Young reported neurological complications of GKT in 8.7% of patients and 6.9% of procedures. Of these, permanent neurological complications were experienced in patients undergoing 3.9% of GKT procedures [6]. For DBS, there are some studies report of the complication. A study reported permanent neurological sequelae in 6% of 86 patients who underwent DBS procedures and 30% of all patients suffered some adverse event as a result of the DBS procedures [14]. A study by Grill reported that permanent neurological sequelae resulted in 4–6% of patients who underwent DBS, and that the overall complication rate can exceed 25% [15].

Anatomical region

Either DBS or GKRS, anatomy structure involved in therapy is VIM. The VIM is thalamic relay nucleus of the cerebellothalamocortical pathway mediating cerebellar control of motor cortex. DBS and GKRS disrupt the function of this pathway [16]. However, there are many opinions about exactly location of VIM.

The location is measured from anterior commissural line (AC), posterior commissural line (PC) and midcommissural (MC). Kondziolka *et al*. state that VIM is bordered by anterior–posterior (1/4 of the AC–PC distance plus 1 mm anterior to the PC), laterality (1/2 the width of the third ventricle plus 11 mm from the AC–PC line), and superior–inferior (isocenter placed 2.5 mm superior to the AC–PC line) [5]. This map of VIM is different with Cho's study that isocenter of irradiation in 15–17 mm lateral to the AC-PC line, 7–8 mm anterior to the PC, and 3–4 mm superior to the AC-PC line. The laterality of the isocenter was carefully adjusted so as to keep it medial to the internal capsule [9].

Niranjan had suggestion about location of VIM in 50% of the width of the third ventricle plus 11 mm lateral to the AC-PC line (X coordinate), 25% of the AC-PC distance (11 or 2 mm) anterior to the PC (Y coordinate), and a radiosurgery isocenter (4 mm collimator) 2 mm superior to the AC-PC line (Z coordinate) [10]. Last, Oh ye set the coordinates of VIM in 7 mm anteriorly (y coordinate), 3−4 mm dorsally on the same plane (z coordinate), including the intercommissural line, and laterally, 2 mm inside the external boundary of the thalamus (x coordinate, usually 15−17 mm from the midsagittal plane) [8], [11]. However, Drummond *et al*. had the difference location. They use subthalamic nucleus (STN) for Parkinson's disease GKRS. The STN location is 11−11.5 mm lateral and 3−4 mm inferior to AC-PC line, and 2−2.5 mm posterior to the MC point [3].

Dosage of GKRS

There is no fix dosage in GKRS for treatment. The dosage also varies from 110 until 150 Gy (Median 120–130 Gy). According Cho, the use of a higher dose associated with a relatively early clinical efficacy, however, related with complications such as hemiparesis or dysarthria was frequently noted with the use of a high dosage, more than 150 Gy [9]. However, there is a study with decided groups, high dose group (160 Gy) and low dose group (120 Gy) [4]. Hence, we suggest the median of studies, we used can be optimal dosage.

Conclusion

GKRS, especially VIM thalamotomy, offers effective and safe alternative for ET and PD. We need more studies with approved method to answer this clinical question accurately. However, the study comparing GKRS and open surgical is still needed.

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