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Study Protocol

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Evaluating the efficacy and safety of tumor treating fields versus laser interstitial thermal therapy in glioblastoma treatment: a comprehensive systematic review and meta-analysis

Marwa SaedAli Emhemed [1,2,*], Roméo Bujiriri Murhega [3], Asogwa Chukwuebuka Stanley[4], Nathan Mugenyi [5], Temitayo Ayantayo [6], Mubarak Jolayemi Mustapha [7], Tangmi Djabo Eric Adrien [2], Mèhomè Wilfried Dossou [8], Jonas Lotanna Ibekwe [9], Nourou Dine Adeniran Bankole [10,11] and Victor Meza Kyaruzi [12]

[1]Faculty of Medicine, University of Tripoli, Tripoli, Libya
[2]Research Department, Association of Future African Neurosurgeons, Yaoundé, Cameroon
[3]Department of Surgery, Provincial General Reference Hospital of Bukavu, Faculty of Medicine, Université Catholique de Bukavu, Bukavu, Democratic Republic of Congo
[4]Department of Medicine and Surgery, Faculty of Clinical Sciences, College of Medicine, University of Ibadan, Ibadan, Oyo State, Nigeria
[5]Faculty of Medicine, Mbarara University of Science and Technology, Mbarara, Uganda
[6]RNZ Neurosciences, Lagos, Nigeria
[7]Faculty of Basic Medical Sciences, University of Ilorin, Ilorin, Nigeria
[8]Department of Neurosurgery, National Hospital of Niamey, Abdou Moumouni University of Niamey, Niamey, Niger
[9]Department of Medicine and Surgery, Faculty of Clinical Sciences, College of Medicine, University of Ibadan, Ibadan, Oyo State, Nigeria
[10]Clinical Investigation Center (CIC), INSERM, Teaching Hospital of Tours, Tours, France
[11]Department of Interventional Neuroradiology, Teaching Hospital of Tours, Tours, France
[12]Department of Surgery, School of Medicine, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

*Correspondence address. Faculty of Medicine, University of Tripoli, Tripoli, Libya. Tel: +218944866632; E-mail: Marwasaad296@gmail.com

Abstract

Tumor Treating Field (TTF) is considered a new treatment option for glioblastoma. Studies in newly diagnosed GBM (ndGBM) patients have demonstrated a good safety profile and improved efficacy. On the other hand, Laser Interstitial Thermal Therapy (LITT) is a minimally invasive method for treating intracranial tumors that are challenging to treat using conventional techniques. Laser Interstitial Thermal Therapy, a minimally invasive method, is the most indicated treatment technique. Its safety and effectiveness, however, have not been thoroughly substantiated in the literature. To create an accurate understanding of which therapy yields better outcomes to glioblastoma patients regarding safety and efficacy, we decided to run a systematic review and meta-analysis on their comparative safety and therapeutic effects in the treatment of glioblastoma. We used standard and extensive Cochrane search methods. The latest search date was June 2nd, 2023. The study period goes from inception to date. We included Randomized Controlled Trials (RCT) or quasi-RCT and all human-based observational studies assessing the comparative safety and therapeutic outcomes of tumor treating fields to laser interstitial thermal therapy in treating glioblastoma patients. We did not include case reports, abstract-only titles, letters to the editor, conference proceedings, articles with missing data, articles in other languages, and those reporting animal studies. Our study compares Tumor Treating Fields' safety and therapeutic effects on Laser Interstitial Thermal therapy in treating glioblastoma.

INTRODUCTION

Background

Glioblastoma multiforme (GBM), a World Health Organization grade IV malignancy in the brain, is one of the worst types of tumors in people [1]. Glioblastomas have been seen to occur more frequently during the last 20 years as a result of longer life expectancies among the general population and easier access to more precise diagnostic technologies like magnetic resonance imaging (MRI) [2].

'Tumor treating fields (TTF)' is a novel therapeutic approach that uses changing electrical fields to give therapy [3]. TTFs, which act locally and non-invasively to stop the development of tumors,

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are provided by transducer arrays positioned on the skin around the growth [4].

According to the United States Food and Drug Administration, GBM can be treated with the TTF [3, 4]. The approval is due to clinical trials and retrospective research that evaluated the effects of treatments on individuals with newly detected and recurrent glioblastoma [4]. Although the FDA approved these studies' findings for both populations, certain members of the neuro-oncology and neurosurgical profession still doubt the TTF [3]. 'Laser Interstitial Thermal Therapy (LITT)' has become an innovative treatment for several brain lesions, including glioblastoma. In order to create regulated thermal damage by heating the tissue around it, this method inserts a laser-tip probe into the centroid of a brain lesion [5–8]. The ablation zone can be continuously monitored and controlled using real-time MRI thermometry [9].

Research question

How do the safety and therapeutic outcomes of TTF compare to those of LITT in the treatment of glioblastoma in terms of overall survival (OS), progression-free survival (PFS) and treatment-associated adverse events?

Objectives

*Primary objectives

- To compare the OS rates of patients with glioblastoma treated with TTF versus those treated with LITT.
- To assess the progression-free survival (PFS) rates in patients with glioblastoma receiving TTF treatment compared to those receiving LITT treatment.
- To evaluate the frequency and severity of treatment-associated adverse events in patients with glioblastoma treated with TTF versus LITT.

*Secondary objectives

- To investigate the impact of TTF and LITT treatments on health-related quality of life (HRQoL) in patients with glioblastoma.
- To assess the cost-effectiveness of TTF versus LITT for glioblastoma treatment.
- To explore the potential biomarkers and molecular profiles associated with treatment response and resistance in glioblastoma patients treated with TTF and LITT.
- To determine the feasibility and patient acceptance of TTF and LITT treatments for glioblastoma in a real-world clinical setting.

METHODS

Period of study

From inception to 20 June 2023.

The population of study

Patients diagnosed with glioblastoma.

Inclusion criteria

All observational and randomized controlled studies describing the treatment of GBM using tumor-treating fields biomarkers and LITT will be included. Studies comparing both treatment modalities will also be included. Only articles written in English will be included.

Exclusion criteria

Case reports of case series, abstract-only articles, letters to the editor, conference proceedings, articles with missing data, articles in a language other than English and those reporting animal studies will be excluded; also, we will exclude previous systematic review or meta-analyses.

Information source

The search for literature will be executed through several electronic databases, including EMBASE, PubMed, Scopus, Web of Science, Cochrane Library, Global Index Medicus, Semantic Scholar and Google Scholar.

keywords: laser interstitial thermal therapy, tumor treating fields, glioblastoma.

Search strategy

The following key strings will be used in various permutations in combination with Boolean operators and filters ('safety'[MeSH Terms] OR 'safety'[All Fields] OR 'safeties'[All Fields]) AND ('therapeutic uses'[MeSH Terms] OR ('therapeutic'[All Fields] AND 'uses'[All Fields]) OR 'therapeutic uses'[All Fields] OR ('therapeutic'[All Fields] AND 'effect'[All Fields]) OR 'therapeutic effect'[All Fields]) AND (('cysts'[MeSH Terms] OR 'cysts'[All Fields] OR 'cyst'[All Fields] OR 'neurofibroma'[MeSH Terms] OR 'neurofibroma'[All Fields] OR 'neurofibromas'[All Fields] OR 'tumor s'[All Fields] OR 'tumoral'[All Fields] OR 'tumorous'[All Fields] OR 'tumor'[All Fields] OR 'neoplasms'[MeSH Terms] OR 'neoplasms'[All Fields] OR 'tumor'[All Fields] OR 'tumors'[All Fields] OR.

'tumoral'[All Fields] OR 'tumorous'[All Fields] OR 'tumors'[All Fields] OR 'tumors'[All Fields]) AND ('therapy'[MeSH Subheading] OR 'therapy'[All Fields] OR 'treat'[All Fields] OR 'treating'[All Fields] OR 'treated'[All Fields] OR 'treats'[All Fields]) AND ('field'[All Fields] OR 'field s'[All Fields] OR 'fields'[All Fields])) AND (('laser s'[All Fields] OR 'lasers'[MeSH Terms] OR 'lasers'[All Fields] OR 'laser'[All Fields] OR 'lasered'[All Fields] OR 'lasering'[All Fields]) AND ('interstitial'[All Fields] OR 'interstitials'[All Fields]) AND ('thermal'[All Fields] OR 'thermalization'[All Fields] OR 'thermalize'[All Fields] OR 'thermalized'[All Fields] OR 'thermalizes'[All Fields] OR.

'thermalizing'[All Fields] OR 'thermally'[All Fields] OR 'thermal s'[All Fields]) AND ('therapeutics'[MeSH Terms] OR 'therapeutics'[All Fields] OR 'therapies'[All Fields] OR 'therapy'[MeSH Subheading] OR 'therapy'[All Fields] OR 'therapies'[All Fields] OR 'therapies'[All Fields])) AND ('glioblastoma'[MeSH Terms] OR 'glioblastoma'[All Fields] OR 'glioblastomas'[All Fields]).

Translations

safety: 'safety'[MeSH Terms] OR 'safety'[All Fields] OR 'safeties'[All Fields].

therapeutic effect: 'therapeutic uses'[MeSH Terms] OR ('therapeutic'[All Fields] AND 'uses'[All Fields]) OR 'therapeutic uses'[All Fields] OR ('therapeutic'[All Fields] AND 'effect'[All Fields]) OR 'therapeutic effect'[All Fields].

Tumor: 'cysts'[MeSH Terms] OR 'cysts'[All Fields] OR 'cyst'[All Fields] OR 'neurofibroma'[MeSH Terms] OR 'neurofibroma'[All Fields] OR 'neurofibromas'[All Fields] OR 'tumor's'[All Fields] OR 'tumoral'[All Fields] OR 'tumorous'[All Fields] OR 'tumor'[All Fields] OR 'neoplasms'[MeSH Terms] OR 'neoplasms'[All Fields] OR 'tumor'[All Fields] OR 'tumor's'[All Fields] OR 'tumoral'[All Fields] OR 'tumorous'[All Fields] OR 'tumors'[All Fields] OR 'tumors'[All Fields].

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Table 1. PubMed electronic database search strategy of 6 June 2023

Search	Query	Results	Time
#7	Search: (tumor treating fields) AND (glioblastoma)	1520	20:29:00
#6	Search: (laser interstitial thermal therapy) AND (glioblastoma)	73	20:28:06
#5	Search: ((((safety) AND (safety)) AND (therapeutic effect)) AND (tumor treating fields)) AND (glioblastoma)	3	20:25:05
#4	Search: ((safety) AND (therapeutic effect)) AND (glioblastoma)	31	20:24:15
#3	Search: ((safety) AND (therapeutic effect)) AND (glioblastoma)	555	20:21:26
#2	Search: (((safety) AND (therapeutic effect)) AND (Laser Interstitial Thermal Therapy)) AND (glioblastoma)	2	20:20:20
#1	Search: ((((safety) AND (therapeutic effect)) AND (Tumor Treating Fields)) AND (Laser Interstitial Thermal Therapy)) AND (glioblastoma)	1	20:19:08

Treating: 'therapy'[Subheading] OR 'therapy'[All Fields] OR 'treat'[All Fields] OR 'treating'[All Fields] OR 'treated'[All Fields] OR 'treats'[All Fields].

Fields: 'field'[All Fields] OR 'field's'[All Fields] OR 'fields'[All Fields].

Laser: 'laser's'[All Fields] OR 'lasers'[MeSH Terms] OR 'lasers'[All Fields] OR 'laser'[All Fields] OR 'lasered'[All Fields] OR 'lasering'[All Fields].

Interstitial: 'interstitial'[All Fields] OR 'interstitials'[All Fields].

Thermal: 'thermal'[All Fields] OR 'thermalization'[All Fields] OR 'thermalize'[All Fields] OR 'thermalized'[All Fields] OR 'thermalizes'[All Fields] OR 'thermalizing'[All Fields] OR 'thermally'[All Fields] OR 'thermals'[All Fields].

Therapy: 'therapeutics'[MeSH Terms] OR 'therapeutics'[All Fields] OR 'therapies'[All Fields] OR 'therapy'[Subheading] OR 'therapy'[All Fields] OR 'therapy's'[All Fields] OR 'therapies'[All Fields].

glioblastoma: 'glioblastoma'[MeSH Terms] OR 'glioblastoma'[All Fields] OR 'glioblastomas'[All Fields] OR 'glioblastoma's'[All Fields] (Table 1).

DATA MANAGEMENT

Study selection

After collecting articles from electronic databases, two reviewers will screen them independently and record the selected articles for full-text screening based on the eligibility criteria. In case of any conflict regarding which article to include, a third-party reviewer will be consulted for a resolution. The PRISMA flow diagram will be employed to present the screened articles, and reasons for exclusion will be justified.

Data extraction

The process will follow Cochrane guidelines [10]. After the full-text screening, two reviewers will extract the needed items for data synthesis; a third-party reviewer will resolve any counterfeit encountered.

Charting data: To ensure all participants in the data extraction step are extracting data homogeneously, we will use an Excel Spreadsheet that includes columns of specific interest for data extraction from eligible studies, such as:

1) General information:

- Publication status.
  - Study title.
- Authors' names.
- Study title, country, the language of publication and year of publication.

2. Study details:

- Aim/purpose of the study.
- Study design/methodology.
- Study population (specifically glioblastoma patients).
- Sample size.
- Duration of interventions.

3. Intervention specifics:

- Comparator used in the study.
- Detailed description of TTField and LITT treatment.

4. Observational parameter:

- OS rates versus LITT.
- PFS rates TTF versus LITT.
- Frequency and severity of treatment-associated adverse events TTF versus LITT.
- Impact of TTF and LITT treatment on HRQoL.
- Cost-effective analysis of TTF versus LITT.
- Identified potential biomarkers and molecular profiles.
- Assessment of feasibility and patient acceptance of TTF and LITT in a real-world setting.

5. Results/key findings.

- Main results directly relate to the study's research question and objectives.

Our approach to charting data is structured and focused on producing a comprehensive and significant summary of relevant information for our rigorous systematic review and meta-analysis.

Data extraction will be carried out in two stages: a pilot stage followed by a proper stage. The pilot stage consists of having multiple authors, each going through the same 10 selected articles to extract data. This is to ensure that all participant authors can extract data accurately for a swift data analysis stage. Piloting this stage is essential to ensure the data collection sheet reflects the included studies.

Data synthesis

The data will be summarized in diagrammatic or tabular form (numerical summary) and a descriptive format (narrative summary). Any commonalities between studies will be synthesized and presented. A qualitative descriptive and quantitative data synthesis will be undertaken on glioblastoma, which is treated by TTF or LITT. The authors will independently assess the quality

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of studies based on the Newcastle-Ottawa Scale [11], a tool for assessing the risk of bias in observational studies [12]. We will report the effect estimates using random-effect models. Publication bias will be assessed using funnel plots and Egger's tests (Egger et al. 1997). Heterogeneity will be evaluated using the Cochrane χ^2 statistic and the I^2 statistic [13]. Depending on the number of studies included, we will perform sensitivity analysis/-subgroup analysis, and meta-regression analysis might be used to explain heterogeneity if applicable.

LIMITATIONS

Despite the comprehensive approach taken by this systematic review and meta-analysis, it is possible that important literature written in a language other than English, as well as data from preclinical studies and other excluded forms of literature, may not have been included and may have been included and may have been overlooked.

ETHICS AND DISSEMINATION

This systematic review of published articles on LITT seeks to be a novel approach to determining the breadth of the literature available on the subject. Therefore, as a secondary analysis, it will not require any ethical approval. We also anticipate that results from this study will reveal research gaps and more profound ideas on the subject, which will be disseminated through journals and conferences.

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CONFLICT OF INTEREST STATEMENT

All authors at this moment declare no conflict of interest.

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We received no funding for the writing of this protocol.

AUTHORS' CONTRIBUTIONS

Marwa SaedAli Emhemed: Conceptualization, Methodology, visualization, writing-original draft. All authors edited and reviewed the manuscript and gave their approval for the manuscript to be published. Victor Meza Kyaruzi: Supervision, validation, writing, review, and editing.

DATA AVAILABILITY

As this is just the protocol for the main study, we agree to share the results of the main study with the journal when available and if judged necessary.

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