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Study Protocol

Study Protocol

The safety and utility of low-intensity pulsed ultrasound for effective blood–brain barrier penetration in the treatment of glioblastoma: a scoping review protocol

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Abstract

Glioblastoma (GBM) is one of the most aggressive central nervous system tumours with suboptimal treatment options and associated poor prognosis. A major impediment to systemic treatment is the limitation of drug delivery to the tumour by the blood-brain barrier (BBB). Several novel techniques to permeate the BBB have been described, however of significant promise is the disruption of the blood brain barrier with low-intensity pulsed ultrasound (LIPU) to facilitate the delivery of varying therapeutic agents. This emerging technique has been demonstrated in clinical studies to enhance delivery of chemotherapeutic agents to the tumour. This study protocol seeks to guide the comprehensive review of literature concerning the safety and utility of LIPU for effective BBB penetration in the treatment of GBM. This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA ScR) guideline 2020. The search strategy was performed on four databases: PubMed, EMBASE, SCOPUS, and Cochrane Central Register of Controlled Trials. All observational and human randomised controlled studies describing the use of LIPU in the treatment of GBM will be included. Excluded studies include non-human randomized control trials, abstract only articles, letters to the editor, conference proceedings. Our outcomes include frequency of LIPU used, duration of intervention, clinical outcomes, complications, and challenges associated with the use of LIPU. This study aims to assess the safety and feasibility of this technique in the management of the GBM and proscribe its use if found effective to improve the outcomes in these patients.

INTRODUCTION

Background

Glioblastoma (GBM) is one of the most aggressive primary central nervous system (CNS) tumors with poor clinical outcomes [1]. GBM frequently recurs despite extensive treatment therapies and current chemotherapy treatments have been demonstrated to be only minimally effective because of minute improvement to the median duration of survival [2]. Clinical trials of varying novel therapeutics have not resulted in increased patient survival [3]. The blood–brain barrier (BBB) has been demonstrated to contribute to the ineffectiveness of chemotherapy for GBM [4].

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The BBB is a specialized physio-biochemical barrier that keeps the brain in a state of balance and shields CNS tissues from hazardous xenobiotics moving through the circulatory system. Most chemotherapy drugs are unable to cross the BBB, which reduces their effectiveness in individuals with GBM [5].

Numerous techniques have been discovered to disrupt the BBB and increase the amount of medications that can get into the brain [5]. Several preclinical trials have demonstrated the use of ultrasound-induced blood–brain barrier opening (US-BBB) to improve the delivery of a broad spectrum of small and large molecule medications into the brain. To achieve this, low-intensity pulsed ultrasound (LIPU) is administered to the brain for some minutes, causing oscillations of intravenously administered micron-sized microbubbles inside the circulatory vasculature [6]. By rupturing the tight connections of endothelium, and enhancing transcytosis, oscillations of microbubbles momentarily expose the BBB for 6–24 h [7, 8].

Several clinical trials have reported enhanced delivery of chemotherapeutic agents such as temozolomide, carmustine, irinotecan, carboplatin, doxorubicin and drug-loaded liposomes via US-BBB opening for the treatment of GBM [9, 10].

Study aims

Primary aims

- To assess the utility of LIPU as a method of effectively penetrating the BBB.
- To assess the safety profile of LIPU as a method of effectively disrupting the BBB integrity.

Secondary aims

- To investigate the potential mechanisms underlying BBB disruption by LIPU.
- To compare the safety profile and effectiveness of LIPU at BBB disruption with other existing methods, such as focused ultrasound, and adenosinergic drugs.
- To assess the clinical outcomes following the use of LIPU in the management of neurological disorders such as GBM.
- To explore the potential use of LIPU in the management of neurological conditions.

METHODOLOGY

This scoping review aims to evaluate the safety and utility of LIPU for effective penetration of the hemato-encephalic barrier in the treatment of GBM. The Preferred Reporting Items for Systematic Review and Meta-Analysis extension for Scoping Reviews guidelines will be used to report the findings [11].

This protocol will be conducted using Arksey and O'Malley's [12] framework that will involve five stages: (i) identify the research question, (ii) identify relevant studies, (iii) select studies, (iv) charting the data and (v) collating, summarizing and reporting the results.

Eligibility criteria

- Period of study:
  The search and study inclusion will include all possible data with a tenure of 10 years from 1 January 2012 to 31 December 2022.
- Inclusion criteria:
  All observational and randomized controlled studies describing safety and utility of LIPU for effective BBB penetration in the treatment of GBM and their predictive values will 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, in languages other than English and those reporting animal studies will be excluded. Studies describing the use of other ultrasound modalities in GBM treatment not including LIPU will be excluded.

Information source

The proposed review will conduct a scoping review for the literature articles utilizing major electronic databases such as PubMed, Cochrane Library, EMBASE and SCOPUS. The selection of these databases is based on their wide-ranging scope and established a reputation for providing authoritative and credible scholarly publications.

Search strategy

The following key strings will be used in various permutation in combination with Boolean operators and filters Ultrasonic waves [MeSH Terms] OR low intensity pulsed ultrasound [MeSH Terms] OR low frequency ultrasound [MeSH Terms] OR low intensity ultrasound [MeSH Terms] OR sonication [MeSH Terms] AND blood brain barrier [MeSH terms] OR cerebrovascular barrier [All fields] OR brain endothelial barrier [All fields] OR blood cerebrospinal fluid barrier [All fields] OR cerebrovascular permeability [All fields] AND Glioblastoma [MeSH terms] (Table 1).

DATA MANAGEMENT

Study selection

After retrieving the search results from all databases, they will be merged into EndNote software, and duplicates detection will be carried by EndNote. The rest of the articles will be exported to Rayyan [13] for conducting initial title and abstract screening independently by four reviewers. Conflicts will be resolved through discussion between the review teams; a different review author will serve as the arbitrator if consensus cannot be reached.

After getting the full-text of all candidate studies, a second phase of full-text screening will be conducted to evaluate the articles for inclusion and to ensure that they meet the inclusion criteria. Also, a final screening will be carried by the time of evaluating the risk of bias of included studies.

References of finally included articles will be manually searched for possible relevant studies, and to make sure that we did not miss any eligible studies.

Data extraction: The data extraction process will involve two stages. An initial pilot extraction will be done. This will involve the random selection of five articles from which the authors will extract data based on the study outcomes and stated objectives. The pilot phase is to ensure the homogeneity of the extraction method, discover ambiguous data or important data that have been omitted. After the pilot phase, authors will meet to discuss and agree on the appropriate data to be extracted. The next phase will involve the main data extraction, where the studies that meet the eligibility criteria will be thoroughly reviewed to extract established data.

Charting the data: To ensure homogeneous data extraction by all participants, a Google Sheets (Google, Mountain View, CA, USA) data extraction form will be used. The following data from the eligible studies will be extracted:

- Author and name of study
- Year of publication

Table 1. PubMed search strategy

Search	Query
#12	Search: #1 OR #2 OR #3 OR #4 OR #5 AND #6 OR #7 OR #8 OR #9 OR #10 AND #11 ((('ultrasonic waves'[MeSH Terms] OR 'ultrasonic waves'[MeSH Terms] OR (('low'[All Fields] AND ('epidemiology'[MeSH Subheading] OR 'epidemiology'[All Fields] OR 'frequency'[All Fields] OR 'epidemiology'[MeSH Terms] OR 'frequence'[All Fields] OR 'frequences'[All Fields] OR 'frequencies'[All Fields])) AND ('ultrasonography'[MeSH Terms] OR 'ultrasonics'[MeSH Terms])) OR (('low'[All Fields] AND ('intense'[All Fields] OR 'intensely'[All Fields] OR 'intensities'[All Fields] OR 'intensity'[All Fields] OR 'intensively'[All Fields])) AND ('ultrasonography'[MeSH Terms] OR 'ultrasonics'[MeSH Terms])) OR 'sonication'[MeSH Terms]) AND 'blood brain barrier'[MeSH Terms]) OR ('cerebrovascular'[All Fields] AND ('barrier'[All Fields] OR 'barrier s'[All Fields] OR 'barriers'[All Fields])) OR (('brain'[MeSH Terms] OR 'brain'[All Fields] OR 'brains'[All Fields] OR 'brain s'[All Fields]) AND ('endothelialization'[All Fields] OR 'endothelialize'[All Fields] OR 'endothelialized'[All Fields] OR 'endothelializing'[All Fields] OR 'endothelials'[All Fields] OR 'endothelium'[MeSH Terms] OR 'endothelium'[All Fields] OR 'endothelial'[All Fields]) AND ('barrier'[All Fields] OR 'barrier s'[All Fields] OR 'barriers'[All Fields])) OR (('blood'[MeSH Subheading] OR 'blood'[All Fields] OR 'blood'[MeSH Terms] OR 'bloods'[All Fields] OR 'haematology'[All Fields] OR 'hematology'[MeSH Terms] OR 'hematology'[All Fields] OR 'haematoma'[All Fields] OR 'hematoma'[MeSH Terms] OR 'hematoma'[All Fields] OR 'haemorrhage'[All Fields] OR 'hemorrhage'[MeSH Terms] OR 'hemorrhage'[All Fields] OR 'haemorrhages'[All Fields] OR 'hemorrhages'[All Fields] OR 'haemorrhagic'[All Fields] OR 'haemorrhaging'[All Fields] OR 'hematologies'[All Fields] OR 'haematomas'[All Fields] OR 'hematomas'[All Fields] OR 'hematoma s'[All Fields] OR 'hematomae'[All Fields] OR 'hemorrhaged'[All Fields] OR 'hemorrhagic'[All Fields] OR 'hemorrhagical'[All Fields] OR 'hemorrhaging'[All Fields]) AND ('cerebrospinal fluid'[MeSH Subheading] OR ('cerebrospinal'[All Fields] AND 'fluid'[All Fields]) OR 'cerebrospinal fluid'[All Fields] OR 'cerebrospinal fluid'[MeSH Terms] OR ('cerebrospinal'[All Fields] AND 'fluid'[All Fields])) AND ('barrier'[All Fields] OR 'barrier s'[All Fields] OR 'barriers'[All Fields])) OR ('cerebrovascular'[All Fields] AND ('permeability'[MeSH Terms] OR 'permeability'[All Fields] OR 'permeabilities'[All Fields] OR 'permeable'[All Fields]))) AND 'glioblastoma'[MeSH Terms] **Translations** **ultrasonic waves[MeSH Terms]:** 'ultrasonic waves'[MeSH Terms] **low intensity pulsed ultrasound[MeSH Terms]:** 'ultrasonic waves'[MeSH Terms] **frequency:** 'epidemiology'[Subheading] OR 'epidemiology'[All Fields] OR 'frequency'[All Fields] OR 'epidemiology'[MeSH Terms] OR 'frequence'[All Fields] OR 'frequences'[All Fields] OR 'frequencies'[All Fields] **ultrasound[MeSH Terms]:** 'ultrasonography'[MeSH Terms] OR 'ultrasonics'[MeSH Terms] **intensity:** 'intense'[All Fields] OR 'intensely'[All Fields] OR 'intensities'[All Fields] OR 'intensity'[All Fields] OR 'intensively'[All Fields] **ultrasound[MeSH Terms]:** 'ultrasonography'[MeSH Terms] OR 'ultrasonics'[MeSH Terms] **sonication[MeSH Terms]:** 'sonication'[MeSH Terms] **blood brain barrier[MeSH Terms]:** 'blood-brain barrier'[MeSH Terms] **barrier:** 'barrier'[All Fields] OR 'barrier's'[All Fields] OR 'barriers'[All Fields] **brain:** 'brain'[MeSH Terms] OR 'brain'[All Fields] OR 'brains'[All Fields] OR 'brain's'[All Fields] **endothelial:** 'endothelialization'[All Fields] OR 'endothelialize'[All Fields] OR 'endothelialized'[All Fields] OR 'endothelializing'[All Fields] OR 'endothelials'[All Fields] OR 'endothelium'[MeSH Terms] OR 'endothelium'[All Fields] OR 'endothelial'[All Fields] **barrier:** 'barrier'[All Fields] OR 'barrier's'[All Fields] OR 'barriers'[All Fields] **blood:** 'blood'[Subheading] OR 'blood'[All Fields] OR 'blood'[MeSH Terms] OR 'bloods'[All Fields] OR 'haematology'[All Fields] OR 'hematology'[MeSH Terms] OR 'hematology'[All Fields] OR 'haematoma'[All Fields] OR 'hematoma'[MeSH Terms] OR 'hematoma'[All Fields] OR 'haemorrhage'[All Fields] OR 'hemorrhage'[MeSH Terms] OR 'hemorrhage'[All Fields] OR 'haemorrhages'[All Fields] OR 'hemorrhages'[All Fields] OR 'haemorrhagic'[All Fields] OR 'haemorrhaging'[All Fields] OR 'hematologies'[All Fields] OR 'haematomas'[All Fields] OR 'hematomas'[All Fields] OR 'hematoma's'[All Fields] OR 'hematomae'[All Fields] OR 'hemorrhaged'[All Fields] OR 'hemorrhagic'[All Fields] OR 'hemorrhagical'[All Fields] OR 'hemorrhaging'[All Fields] **cerebrospinal fluid:** 'cerebrospinal fluid'[Subheading] OR ('cerebrospinal'[All Fields] AND 'fluid'[All Fields]) OR 'cerebrospinal fluid'[All Fields] OR 'cerebrospinal fluid'[MeSH Terms] OR ('cerebrospinal'[All Fields] AND 'fluid'[All Fields]) **barrier:** 'barrier'[All Fields] OR 'barrier's'[All Fields] OR 'barriers'[All Fields] **permeability:** 'permeability'[MeSH Terms] OR 'permeability'[All Fields] OR 'permeabilities'[All Fields] OR 'permeable'[All Fields] **glioblastoma[MeSH Terms]:** 'glioblastoma'[MeSH Terms]
#11	Search: **glioblastoma[MeSH Terms]** 'glioblastoma'[MeSH Terms] **Translations** **glioblastoma[MeSH Terms]:** 'glioblastoma'[MeSH Terms]
#10	Search: **cerebrovascular permeability** 'cerebrovascular'[All Fields] AND ('permeability'[MeSH Terms] OR 'permeability'[All Fields] OR 'permeabilities'[All Fields] OR 'permeable'[All Fields]) **Translations** **permeability:** 'permeability'[MeSH Terms] OR 'permeability'[All Fields] OR 'permeabilities'[All Fields] OR 'permeable'[All Fields]
#9	Search: **blood cerebrospinal fluid barrier** ('blood'[MeSH Subheading] OR 'blood'[All Fields] OR 'blood'[MeSH Terms] OR 'bloods'[All Fields] OR 'haematology'[All Fields] OR 'hematology'[MeSH Terms] OR 'hematology'[All Fields] OR 'haematoma'[All Fields] OR 'hematoma'[MeSH Terms] OR 'hematoma'[All Fields] OR 'haemorrhage'[All Fields] OR 'hemorrhage'[MeSH Terms] OR 'hemorrhage'[All Fields] OR 'haemorrhages'[All Fields] OR 'hemorrhages'[All Fields] OR 'haemorrhagic'[All Fields] OR 'haemorrhaging'[All Fields] OR 'hematologies'[All Fields] OR 'haematomas'[All Fields] OR 'hematomas'[All Fields] OR 'hematoma s'[All Fields] OR 'hematomae'[All Fields] OR 'hemorrhaged'[All Fields] OR 'hemorrhagic'[All Fields] OR 'hemorrhagical'[All Fields] OR 'hemorrhaging'[All Fields]) AND ('cerebrospinal fluid'[MeSH Subheading] OR ('cerebrospinal'[All Fields] AND 'fluid'[All Fields]) OR 'cerebrospinal fluid'[All Fields] OR 'cerebrospinal fluid'[MeSH Terms] OR ('cerebrospinal'[All Fields] AND 'fluid'[All Fields])) AND ('barrier'[All Fields] OR 'barrier s'[All Fields] OR 'barriers'[All Fields])

(*Continued*)

Table 1. PubMed search strategy

Search	Query
	Translations **blood:** 'blood'[Subheading] OR 'blood'[All Fields] OR 'blood'[MeSH Terms] OR 'bloods'[All Fields] OR 'haematology'[All Fields] OR 'hematology'[MeSH Terms] OR 'hematology'[All Fields] OR 'haematoma'[All Fields] OR 'hematoma'[MeSH Terms] OR 'hematoma'[All Fields] OR 'haemorrhage'[All Fields] OR 'hemorrhage'[MeSH Terms] OR 'hemorrhage'[All Fields] OR 'haemorrhages'[All Fields] OR 'hemorrhages'[All Fields] OR 'haemorrhagic'[All Fields] OR 'haemorrhaging'[All Fields] OR 'hematologies'[All Fields] OR 'haematomas'[All Fields] OR 'hematomas'[All Fields] OR 'hematoma's'[All Fields] OR 'hematomae'[All Fields] OR 'hemorrhaged'[All Fields] OR 'hemorrhagic'[All Fields] OR 'hemorrhagical'[All Fields] OR 'hemorrhaging'[All Fields] **cerebrospinal fluid:** 'cerebrospinal fluid'[Subheading] OR ('cerebrospinal'[All Fields] AND 'fluid'[All Fields]) OR 'cerebrospinal fluid'[All Fields] OR 'cerebrospinal fluid'[MeSH Terms] OR ('cerebrospinal'[All Fields] AND 'fluid'[All Fields]) **barrier:** 'barrier'[All Fields] OR 'barrier's'[All Fields] OR 'barriers'[All Fields]
#8	Search: **brain endothelial barrier** ('brain'[MeSH Terms] OR 'brain'[All Fields] OR 'brains'[All Fields] OR 'brain s'[All Fields]) AND ('endothelialization'[All Fields] OR 'endothelialize'[All Fields] OR 'endothelialized'[All Fields] OR 'endothelializing'[All Fields] OR 'endothelials'[All Fields] OR 'endothelium'[MeSH Terms] OR 'endothelium'[All Fields] OR 'endothelial'[All Fields]) AND ('barrier'[All Fields] OR 'barrier s'[All Fields] OR 'barriers'[All Fields]) **Translations** **brain:** 'brain'[MeSH Terms] OR 'brain'[All Fields] OR 'brains'[All Fields] OR 'brain's'[All Fields] **endothelial:** 'endothelialization'[All Fields] OR 'endothelialize'[All Fields] OR 'endothelialized'[All Fields] OR 'endothelializing'[All Fields] OR 'endothelials'[All Fields] OR 'endothelium'[MeSH Terms] OR 'endothelium'[All Fields] OR 'endothelial'[All Fields] **barrier:** 'barrier'[All Fields] OR 'barrier's'[All Fields] OR 'barriers'[All Fields]
#7	Search: **cerebrovascular barrier** 'cerebrovascular'[All Fields] AND ('barrier'[All Fields] OR 'barrier s'[All Fields] OR 'barriers'[All Fields]) **Translations** **barrier:** 'barrier'[All Fields] OR 'barrier's'[All Fields] OR 'barriers'[All Fields]
#6	Search: **blood brain barrier[MeSH Terms]** 'blood brain barrier'[MeSH Terms] **Translations** **blood brain barrier[MeSH Terms]:** 'blood-brain barrier'[MeSH Terms]
#5	Search: **sonication[MeSH Terms]** 'sonication'[MeSH Terms] **Translations** **sonication[MeSH Terms]:** 'sonication'[MeSH Terms]
#4	Search: **low intensity ultrasound[MeSH Terms]** ('low'[All Fields] AND ('intense'[All Fields] OR 'intensely'[All Fields] OR 'intensities'[All Fields] OR 'intensity'[All Fields] OR 'intensively'[All Fields])) AND ('ultrasonography'[MeSH Terms] OR 'ultrasonics'[MeSH Terms]) **Translations** **intensity:** 'intense'[All Fields] OR 'intensely'[All Fields] OR 'intensities'[All Fields] OR 'intensity'[All Fields] OR 'intensively'[All Fields] **ultrasound[MeSH Terms]:** 'ultrasonography'[MeSH Terms] OR 'ultrasonics'[MeSH Terms]
#3	Search: **low frequency ultrasound[MeSH Terms]** ('low'[All Fields] AND ('epidemiology'[MeSH Subheading] OR 'epidemiology'[All Fields] OR 'frequency'[All Fields] OR 'epidemiology'[MeSH Terms] OR 'frequence'[All Fields] OR 'frequences'[All Fields] OR 'frequencies'[All Fields])) AND ('ultrasonography'[MeSH Terms] OR 'ultrasonics'[MeSH Terms]) **Translations** **frequency:** 'epidemiology'[Subheading] OR 'epidemiology'[All Fields] OR 'frequency'[All Fields] OR 'epidemiology'[MeSH Terms] OR 'frequence'[All Fields] OR 'frequences'[All Fields] OR 'frequencies'[All Fields] **ultrasound[MeSH Terms]:** 'ultrasonography'[MeSH Terms] OR 'ultrasonics'[MeSH Terms]
#2	Search: **low intensity pulsed ultrasound[MeSH Terms]** 'ultrasonic waves'[MeSH Terms] **Translations** **low intensity pulsed ultrasound[MeSH Terms]:** 'ultrasonic waves'[MeSH Terms]
#1	Search: **ultrasonic waves[MeSH Terms]** 'ultrasonic waves'[MeSH Terms] **Translations** **ultrasonic waves[MeSH Terms]:** 'ultrasonic waves'[MeSH Terms]

- Country of origin
- Study population and sample size
- Intervention type and comparator
- Duration of intervention if present
- Frequency of LIPU used
- Clinical outcomes and measures if present
- Overall survival and progression-free survival
- Complications
- Associated challenges with the use of LIPU

Data synthesis

The extracted data will be synthesized, and results obtained will be summarized using tables and figures. A narrative summary

will be added to describe these results. Similarities between studies shall be pointed out, synthesized, and presented. Data from individual studies and pooled results will be expressed as means with 95% confidence intervals.

LIMITATIONS

We may miss the relevant literature not written in English and information captured in preclinical studies and other excluded forms of the literature.

ACKNOWLEDGEMENTS

We acknowledge the Evidence-Based Scientific Consortium (EBSC) for supporting this study.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

ETHICS AND DISSEMINATION

This scoping review on the safety and utility of (LIPU) for effective BBB penetration in the treatment of GBM is a novel approach for determining the breadth of the literature available on the subject and identifying the nature and extent of research evidence, therefore, as a scoping review, 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 and these results shall be disseminated through journals and conferences relevant to the topic.

AUTHORS' CONTRIBUTION

All authors contributed equally to the writing of this protocol.

GRANT SUPPORT

None.

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