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Corresponding author:
Annemiek Hogenes

annemiek.hogenes@radboudumc.nl

Author Affiliation:
Radboud University Medical Center, Nijmegen, The Netherlands.

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None declared.

The Influence of Irreversible Electroporation Parameters on the Size of the Ablation Zone and Thermal Effects: a Systematic Review

Hogenes, AM[1]; Overduin, CG[2]; Slump, CH[3]; van Laarhoven, CJHM[4]; Fütterer, JJ[5]; ten Broek, RPG[6]; Stommel, MWJ[7].

Review question / Objective: **The aim of this study was to review the effect of irreversible electroporation (IRE) parameter settings on the size of the ablation zone and occurrence of thermal effects.**
Information sources: **A search was performed in PubMed (also including MEDLINE), Web of Science, Embase, Institute of Electrical and Electronics Engineers (IEEE) Xplore Digital Library and American Society of Mechanical Engineers (ASME) Digital Collection. Of all conference abstracts of which no full text article was present in the title and abstract search, a web-based search (Google Scholar, ResearchGate, author and co-author name(s) in Embase) was done to investigate whether a full text article was available. A manual search of the reference lists of relevant (included) articles was performed to find articles which were not found by the initial search. The corresponding author was approached by e-mail (in case the contact details were available) when the full text of a relevant abstract (e.g. conference abstract) could not be found to verify whether the results were published as full text. The study was excluded when the full text could not be found or provided.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 March 2022 and was last updated on 29 March 2022 (registration number INPLASY202230161).

INTRODUCTION

Review question / Objective: **The aim of this study was to review the effect of irreversible electroporation (IRE) parameter settings on the size of the ablation zone and occurrence of thermal effects.**

Rationale: **Irreversible electroporation (IRE) theoretically is a non-thermal ablation**

technique. A high voltage pulsed electric field with a threshold of 680 V/cm is used to permanently permeabilize tumor cells. Resulting in an imbalance in ions inside and outside the cell and cell death due to loss of homeostasis. Critical structures, such as blood vessels and nerves, are spared since the extracellular matrix is remained intact during treatment. Therefore, IRE is an interesting technique for solid tumor ablation. For example, in the treatment of locally advanced pancreatic cancer (LAPC) and hepatic tumors near the bile duct. Blood vessels are encased by tumor tissue in LAPC. From previous research is known that thermal effects or damage may occur in vicinity of the needle-electrodes. That could be a problem since vital structures, blood vessels in the case of LAPC, are located near the needle-electrodes. Therefore, the aim of this review is to investigate the effect of variation in electroporation parameter settings on the occurrence of thermal effects. In line with this question, standard IRE parameter settings are often used to treat a patient. However, for a personalized treatment and to obtain the insight how to react when a technical issue occurs during the procedure, it is important to know what the influence of each parameter on the ablation zone size. To be able to create an ablation zone which is as large as possible while preventing the occurrence of thermal effects. This systematic review provides an overview of this topic.

Condition being studied: No actual condition is studied in this review. The relation between (irreversible) electroporation parameter settings and the size of the ablation zone and occurrence of thermal effects was investigated.

METHODS

Search strategy: PubMed (and MEDLINE)
The search was performed in the "Advanced search" mode. NanoKnife[tiab] OR Irreversible electroporation*[tiab] OR Reversible electroporation*[tiab] OR ((Non-thermal[tiab] OR Nonthermal[tiab]) AND Ablation[tiab]) OR Electropermeabili*[tiab] OR Pulsed electric field*[tiab] OR Pulsed electrical field*[tiab] OR Pulse electric field*[tiab] OR Pulse electrical field*[tiab]
Web of Science
The search was performed in the "Advanced search" mode. No restrictions were added to the search.
TS = (NanoKnife OR Irreversible electroporation* OR Reversible electroporation* OR ((Non-thermal OR Nonthermal) AND Ablation) OR Electropermeabili*)
Embase
The search was performed in the "Advanced search" mode.
Irreversible electroporation/
OR Irreversible electroporation device/
OR (NanoKnife OR Irreversible electroporation* OR Reversible electroporation* OR ((Non-thermal or nonthermal) AND ablation) OR Electropermeabili* OR Pulsed electric field* OR Pulsed electrical field* OR Pulse electric field* OR Pulse electrical field*).ti,ab,kw).af
Institute of Electrical and Electronics Engineers (IEEE) Xplore Digital Library
The search was performed in the "Advanced search" mode for all metadata. No restrictions were added to the search. Electroporation was used as a Mesh term.
"All Metadata":NanoKnife OR Irreversible electroporation* OR Reversible electroporation* OR ((Non-thermal OR nonthermal) AND ablation) OR Electropermeabili* OR Electroporation OR "Mesh_Terms":Electroporation
American Society of Mechanical Engineers (ASME) Digital Collection
The search was performed in the "All Content" mode. Electroporation.

Participant or population: Humans, animals (in vivo and ex vivo) and phantom models.

Intervention: Variation in electroporation parameters.

Comparator: Not applicable.

Study designs to be included: No restrictions in study designs. All available study designs could be included, ranging from fundamental research to a RCT.

Eligibility criteria: Studies were included when all eligibility criteria were met. Inclusion criteria were: (a) ablation zone and/or temperature measurements were performed; (b) during or after IRE or RE; (c) performed in in vivo or ex vivo liver, pancreas, kidneys or prostate or electroporation of potato or tissue phantoms; (d) all electroporation parameter settings (voltage, number of electrodes, inter-electrode distance, active needle length, number of pulses and pulse length); and (e) their exact values used for electroporation (e.g. a range, mean or maximum parameter value are not adequate enough) were described; (f) one parameter was consecutively varied during the electroporation while the other parameters were kept constant and (g) the measured ablation zone sizes and temperatures were described for the consecutive variation per studied electroporation parameter. Exclusion criteria were: (a) needle types other than monopolar electrodes to align with the clinical practice (e.g. bipolar electrodes); (b) aberrant needle electrode shapes deviating from a straight needle (e.g. plate or flexible endoscopic electrodes (intraluminal electroporation), electrodes used in combination with a grounding pad or other kind of grounding material instead of another electrode); (c) electroporation in vitro, on (single) cell level or performed with the goal to deliver genes, drugs or chemotherapeutics (electrochemotherapy) into the cell. Other phantom models, such as potato tubers and (polyacrylamide) gel phantoms, are eligible for inclusion; (d) combination therapy (e.g. electrochemotherapy); (e) pulse forms other than monopolar square wave pulses (e.g. bipolar, H-FIRE, exponential decay or sinus formed pulses); (f) simulation models; (g) undefined orientation of the measured ablation zone size with reference to the needle insertion path; (h) metal stents or objects in the electroporation zone; (i) ablation zone and temperature results that were only presented in figures, unable to precisely determine the results; (j) review articles; (k) conference abstracts; and (l) studies published in another language than English, French or German. Of all conference abstracts of which no full text article was present in the title abstract search yet, a web-based search (Google Scholar, ResearchGate, author and co-author name(s) in Embase) was done to investigate whether a full text article was available. The corresponding author was approached by e-mail (in case the contact details were available) when the full text of a relevant abstract (e.g. conference abstract) could not be found to verify whether the results were published as full text. The study was excluded when the full text could not be found or provided.

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Main outcome(s): The main outcomes of this review are: - Ablation zone size (length/surface/volume). Length and surface measured perpendicular to the needle-electrode insertion path) - Temperature (absolute (T) or relative temperature (delta T)) Both outcomes are measured during or after the ablation procedure.

Additional outcome(s): Data on the study model, electroporated organ or phantom, ablation of healthy or tumor tissue, electrode location, electroporation

equipment, electroporation parameter values, method to assess and measure the ablation zone size as well as the method and location of the temperature measurements were extracted from the included studies.

Data management: Duplicates were removed in EndNote X8™ following the method described by Bramer et al. (2016). All de-duplicated titles and abstracts were assessed in Rayyan, a web app developed for systematic review screening, for remaining duplicates and were assessed on eligibility based on predefined in- and exclusion criteria. Two authors independently reviewed a random sample of 650 articles for eligibility by title and abstract screening. Consensus was reached on discordant judgements. The remaining articles were screened by the first author when the inter-rater agreement was >95%. In case of any uncertainty to determine the eligibility, the abstract was independently assessed by and discussed with the second author. Articles included during title and abstract screening were assessed in more detail on eligibility during the full text screening phase. The full text screening was performed by the first author and randomly verified by the second author. Per varied electroporation parameter, the ablation zone size and temperature results were reported. The extracted data was listed in Excel. SPSS version 25 (SPSS, Armonk, NY: IBM Corp) and Microsoft Excel were used for data analysis. The data extraction was performed by the first author and randomly verified by the second author.

Quality assessment / Risk of bias analysis: Assessment of the methodological quality of papers is an important aspect of systematic reviews. Previously validated quality scores for systematic reviews did not fully apply to the types of studies included. Therefore, a specific score was developed for use in this study. Components from the Newcastle-Ottawa Scale, Jadad scale and Cochrane guidelines were used. The following domains were incorporated in the quality assessment score: the study model, sample size, statistical method, the presence of a replicable description of the methods section, ethical approval obtained, availability of the raw data of the ablation zone and temperature results, whether all hypotheses stated per included article were investigated and whether the conclusion was justified by the results.

Strategy of data synthesis: An overview of the influence of variation in electroporation parameter settings on the ablation zone size and occurrence of thermal effects was provided. Ablation zone size and temperature results provided by different models (humane/animal/phantom models) were plotter per varied electroporation parameter. The distribution was assessed based on the study design and sample size in combination with the Kolmogorov-Smirnov test. In case of an explorative study character and small number of observations per electroporation parameter combination, a normal distribution could not be assumed and indicates the use of non-parametric tests. The Spearman correlation coefficient (rho) was used to assess the relationship between the electroporation parameters and the ablation zone size and thermal effects. Only in the cases where $\rho \geq 0.70$ and a trend between the datapoints was observed for that specific electroporation parameter, linear regression was performed.

Subgroup analysis: Both the ablation zone size and temperature results were presented per varied electroporation parameter for all models (human/animal/phantom models) that investigated the effect of that specific parameter on the ablation zone size and/or temperature. The ablation zone size results were subdivided in length, surface and volume outcomes. The temperature results were subdivided in absolute and relative temperature results.

Sensitivity analysis: A sensitivity analysis was not applicable to this systematic review.

Language: Studies published in another language than English, French or German were excluded.

Country(ies) involved: This systematic review was carried out in The Netherlands.

Keywords: Irreversible electroporation; Permeabilization; Pulsed electric field; Ablation; Focal treatment; Cancer therapy; Temperature; Animal model; Phantom model.

Dissemination plans: The results of this systematic review will be disseminated by submission to and publication in a journal where the intended scientific community which performs IRE is reached.

Contributions of each author:

Author 1 - Annemiek Hogenes - A.M.H.: Conceptualization, Methodology, Investigation, Formal Analysis, Visualization, Writing – Original Draft, Project Administration.
Email: annemiek.hogenes@radboudumc.nl
Author 2 - Christiaan Overduin - C.G.O.: Methodology, Investigation, Visualization, Writing – Review & Editing.
Email: kristian.overduin@radboudumc.nl
Author 3 - Cornelis Slump - C.H.S.: Methodology, Visualization, Writing – Review & Editing, Supervision
Email: c.h.slump@utwente.nl
Author 4 - Cornelis van Laarhoven - C.J.H.M.L.: Conceptualization, Writing – Review & Editing.
Email: kees.vanlaarhoven@radboudumc.nl
Author 5 - Jurgen Fütterer - J.J.F.: Conceptualization, Writing – Review & Editing, Supervision.
Email: jurgen.futterer@radboudumc.nl
Author 6 - Richard ten Broek - R.P.G.B.: Methodology, Formal Analysis, Visualization, Writing – Review & Editing.
Email: richard.tenbroek@radboudumc.nl
Author 7 - Martijn Stommel - R.P.G.B.: Methodology, Formal Analysis, Visualization, Writing – Review & Editing.
Email: martijn.stommel@radboudumc.nl