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Early interventions for the prevention of post-traumatic stress symptoms in survivors of critical illness: protocol for a systematic review

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ABSTRACT

Introduction: Post-traumatic stress disorder (PTSD) is being increasingly reported among survivors of critical illness and injury. Previous work has demonstrated that PTSD reduces patient quality of life and ability to return to work, as well as increases health care costs. As such, identifying interventions aimed at preventing the development of critical illness related PTSD could have an important public health impact. The objective of this systematic review is to collate the world's literature on early interventions aimed at preventing PTSD among survivors of critical illness.

Methods and analysis: We will perform a qualitative systematic review of human clinical trials of interventions aimed at preventing or reducing critical illness related PTSD symptoms. We will methodically search CENTRAL, MEDLINE, EMBASE, and CINAHL. We will also search websites containing details on clinical trials registration (National Library of Medicine – ClinicalTrials.gov and the World Health Organization – International Clinical Trials Registry Platform), as well as screen reference lists of the articles we select for inclusion to identify additional studies for potential inclusion. Two authors will independently review all search results. After identification and inclusion of articles, we will use a standardized form for data extraction. We will use tables to describe the study populations, interventions tested and timing of interventions, outcome measures, and effects of interventions on outcome measures compared to control groups.

Ethics and dissemination: The proposed systematic review will not collect individual patient level data and does not require ethical approval. Results of this study will contribute to the understanding of critical illness related PTSD, and help prompt future research aimed at further developing interventions to prevent PTSD symptoms in survivors of critical illness.

Registration: This systematic review is registered in the PROSPERO international prospective register of systematic reviews.

Word count: 283

Keywords: post-traumatic distress syndrome, PTSD, prevention, critical care, systematic review

Strengths:

- This protocol design is consistent with the Cochrane handbook for systematic reviews of interventions, as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement.
- This protocol design is focused on the development of post-traumatic stress disorder secondary to civilian hospitalization, as opposed to a traumatic event outside of the hospital setting.

Limitations:

- Given the likely heterogeneity in both interventions and outcome measures it is unlikely that it will be possible to pool data.

Introduction

Post-traumatic stress disorder (PTSD) is being increasingly reported among survivors of critical illness. It is currently estimated that 25% of critical illness survivors suffer from PTSD,(1) with the incidence among certain populations approaching 65%.(2) PTSD is defined as the development of mental health concerns in someone who is directly or indirectly exposed to a traumatic event. More specifically, trauma is operationalized as someone who is exposed to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence. Subsequently, the individual develops symptoms from each of four symptom clusters, intrusive thoughts or memories, avoidance of trauma-related stimuli, negative alterations in cognitions and mood, and alterations in arousal and reactivity.(3) Critical illness is by definition a life threatening experience, which predisposes many patients to these chronic psychological symptoms. Previous work has demonstrated that patients suffering from PTSD are more likely to have poor physical health-related quality of life with higher frequency and severity of general health symptoms and conditions, such as musculoskeletal pain, cardio-respiratory symptoms, and gastrointestinal symptoms.(4) Furthermore, PTSD is independently associated with the inability to return to work 12 months after intensive care unit (ICU) discharge,(5) as well as increased healthcare costs.(6) As such, preventing the development of PTSD could have an enormous influence on long-term patient outcomes as well as public health.

The development of critical illness related PTSD has been linked to patient experience during medical care. Specifically, frightening experiences(7) and acute psychological stress during resuscitation care are strongly associated with the development of PTSD.(8) A central mechanism to the development of PTSD is the process by which traumatic memories are formed.(9) For many patients frightening experiences result in peri-traumatic dissociation, defined as an alteration in time or place with reported feelings of depersonalization, altered perceptions of pain, feeling disconnected, or tunnel vision.(10) This dissociation has been demonstrated to increase the risk for developing PTSD, [10] likely by causing traumatic

information to be encoded in somatosensory, affective, nonlinguistic, and relatively uncontrolled fragmented memories.(11) Our overarching hypothesis is that interventions, which focus on decreasing the degree of acute stress (i.e. frightening experiences) and dissociation during the traumatic event in the hospital, will shift traumatic information processing from developing uncontrollable fragmented memory, to a more controllable and cognitive memory process, and thus prevent or reduce PTSD severity in survivors of critical illness.

The first step towards testing this hypothesis is to collate the world's literature on interventions aimed at preventing or reducing PTSD symptoms in patients who survive medical emergencies. We hypothesize that there are currently few or no interventions aimed at reducing the degree of acute stress and dissociation, during the traumatic event in the hospital, in order to prevent chronic PTSD in this population.

Methods and analysis

Protocol and registration

This systematic review protocol is prepared in accordance with the Cochrane handbook for systematic reviews of interventions,(12) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement.(13) The final results will be reported according to PRISMA and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.(14, 15) This systematic review has been registered in the PROSPERO international prospective register of systematic reviews.

Search for and identification of studies

An electronic search will include the following databases: CENTRAL, MEDLINE, EMBASE, and CINAHL. The search terms include the concepts of post-traumatic stress, critical

care, and prevention. These strategies were established using a combination of standardized terms and key words, and was modeled after a previously published systematic review examining the prevalence of ICU related PTSD.(2) The fully reproducible search strategy is provided in the online supplement. In order to identify potentially unpublished data from clinical trials we will search websites containing details on clinical trials registration (National Library of Medicine – ClinicalTrials.gov and the World Health Organization – International Clinical Trials Registry Platform). Registered but unpublished trials will be considered eligible for inclusion if the registration website indicates that enrollment in the clinical trial had been completed. We will also screen reference lists of the articles we select for inclusion to identify additional studies for potential inclusion.

Eligibility criteria

We will include all human clinical trials of interventions to prevent PTSD in the critically-ill and injured. In order to be included all studies must contain (1) adult patients diagnosed with a critical illness or injury; (2) patients treated in an emergency department or ICU setting; (3) an intervention arm in which subjects clearly underwent an intervention aimed at preventing or reducing PTSD symptoms, as the single experimental intervention; (4) a clearly defined control arm in which subjects received placebo or standard of care therapy; and (5) an outcome measure assessing development of acute stress or PTSD symptoms. We will consider studies eligible for review regardless of language or publication type. We will exclude studies that are secondary reports of previously published trials. We also will exclude papers that are reviews, correspondence, or editorials; however, we will screen the reference lists of review articles to identify further studies for inclusion.

Study selection and data abstraction

Two independent reviewers will screen the titles and abstracts of identified studies for potential eligibility. After the relevance screen, the two reviewers will compare their exclusion logs to determine whether there is disagreement and use the Kappa statistic to quantify the inter-observer agreement. In cases of disagreement, a third reviewer will assess the abstract and a consensus will be reached by conference between the three reviewers. All studies deemed potentially relevant will be obtained and the full manuscripts will be reviewed for inclusion. Two reviewers will independently abstract data on all patient populations, interventions and timing of interventions, outcome measures, adverse events, and results using a standardized data collection form. Any disagreements in these processes will be resolved by consensus with a third reviewer.

Assessment of study bias

For each clinical trial, we will assess the quality of the studies selected for inclusion using the Cochrane Collaboration's tool for assessing the risk of bias in clinical trials evaluating six domains (selection, performance, detection, attrition, reporting, and other biases).(12)

Analysis

We will perform a primarily qualitative analysis of the data in accordance with the recommended methodology for qualitative reviews published in the Cochrane Handbook.(12) We will collate and summarize clinical trials in table format, stratified by individual publication. We will table: (1) population sampled (e.g. motor vehicle crash, sepsis patients), (2) description of intervention performed, (3) timing of intervention, (5) outcome measures, including primary and all secondary outcomes, and (4) effect of intervention on outcome measures compared to control groups.

Given the likely heterogeneity in both interventions and outcome measures it is unlikely that it will be possible to pool data. However, if after conducting the systematic review it is determined data can be pooled, we will perform meta-analyses using random effects models to calculate overall effect sizes and 95% confidence intervals between intervention and control groups. For binary data, such as development of PTSD (yes/no), odds ratios will be calculated, and for continuous outcomes mean differences will be reported. A p value of < 0.05 will be considered statistically significant. Finally, the I^2 statistic will be used to assess heterogeneity between studies. We will consider the following thresholds for the I^2 statistic: low (25-49%), moderate (50-74%), and high (≥75%) values.(16)

Protocol amendments

If an amendment to this protocol is required, the date of each amendment will be accompanied by a description of the change along with the rationale.

Ethics and dissemination

No ethical approval will be required for this systematic review of completed studies. Results from this systematic review will be submitted to peer-reviewed journals for publication, and to national meetings in presentation form. We anticipate that this study will identify a need for further research aimed at developing early interventions to prevent or reduce PTSD symptoms in survivors of critical illness.

Discussion

There has been an increasing understanding that emotional trauma in the form of PTSD is common among patients who experience serious health emergencies and survive critical illness. PTSD has been shown to have long-lasting effects on physical and emotional well-being,(4) along with increasing healthcare costs.(6) However, it is currently unclear if early

interventions can prevent or reduce emotional trauma in patients suffering from health emergencies.

This systematic review will collate the world's literature of early interventions aimed at preventing the development of PTSD in survivors of critical illness. We expect to find that there are currently few or no interventions aimed at reducing the degree of acute stress and dissociation, during the traumatic event in the hospital, in order to prevent chronic PTSD in this population. Specifically, we will identify important knowledge gaps in the literature.

In conclusion, results of this study will contribute to the understanding of critical illness related PTSD, and help prompt future research aimed at further developing interventions to prevent PTSD symptoms in survivors of critical illness.

References

1. Wade D, Hardy R, Howell D, et al. Identifying clinical and acute psychological risk factors for PTSD after critical care: a systematic review. Minerva Anestesiol 2013;79(8):944-963.

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16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539-1558.

Author contributions: All authors have made substantial contributions to this paper. BWR supervised all aspects of the study design and takes responsibility for the paper as a whole. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. MBR and BWR developed the search strategy. BWR provided statistical expertise. LG and BWR drafted the manuscript. All authors read and contributed substantially to revision of the final manuscript. All authors approved the manuscript in its final form.

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ABSTRACT

Introduction: Post-traumatic stress disorder (PTSD) is being increasingly reported among survivors of critical illness and injury. Previous work has demonstrated that PTSD reduces patient quality of life and ability to return to work, as well as increases health care costs. As such, identifying interventions aimed at preventing the development of critical illness related PTSD could have an important public health impact. The objective of this systematic review is to collate the world's literature on early interventions aimed at preventing PTSD among survivors of critical illness.

Methods and analysis: We will perform a qualitative systematic review of human clinical trials of interventions aimed at preventing or reducing critical illness related PTSD symptoms. We will methodically search CENTRAL, MEDLINE, EMBASE, and CINAHL. We will also search websites containing details on clinical trials registration (National Library of Medicine – ClinicalTrials.gov and the World Health Organization – International Clinical Trials Registry Platform), as well as screen reference lists of the articles we select for inclusion to identify additional studies for potential inclusion. Two authors will independently review all search results. After identification and inclusion of articles, we will use a standardized form for data extraction. We will use tables to describe the study type, populations, interventions tested and timing of interventions, outcome measures, and effects of interventions on outcome measures compared to control groups. This review will be completed between 8/1/2017 and 8/31/2017.

Ethics and dissemination: The proposed systematic review will not collect individual patient level data and does not require ethical approval. Results of this study will contribute to the understanding of critical illness related PTSD, and help prompt future research aimed at further developing interventions to prevent PTSD symptoms in survivors of critical illness.

Registration: This systematic review is registered in the PROSPERO international prospective register of systematic reviews.

Word count: 295

Keywords: post-traumatic distress syndrome, PTSD, prevention, critical care, systematic review

Strengths

- This systematic review will be the first comprehensive search of the literature to identify and describe early interventions aimed at preventing intensive care unit (ICU) related post-traumatic stress disorder.
- Experts in the field, including a clinical psychologist and intensivists, with experience performing systematic reviews, developed our search strategy.
- We plan to perform an exhaustive search of multiple databases (i.e. CENTRAL, MEDLINE, EMBASE, and CINAHL).

Limitations

- It is highly likely that we will find a paucity of data on early interventions aimed at preventing intensive care unit (ICU) related post-traumatic stress disorder.

Introduction

Post-traumatic stress disorder (PTSD) is being increasingly reported among survivors of critical illness. It is currently estimated that 25% of critical illness survivors suffer from PTSD,(1) with the incidence among certain populations approaching 65%.(2) PTSD is defined as the development of mental health concerns in someone who is directly or indirectly exposed to a traumatic event. More specifically, trauma is operationalized as someone who is exposed to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence. Subsequently, the individual develops symptoms from each of four symptom clusters, intrusive thoughts or memories, avoidance of trauma-related stimuli, negative alterations in cognitions and mood, and alterations in arousal and reactivity.(3) Critical illness is by definition a life threatening experience, which predisposes many patients to these chronic psychological symptoms. Previous work has demonstrated that patients suffering from PTSD are more likely to have poor physical health-related quality of life with higher frequency and severity of general health symptoms and conditions, such as musculoskeletal pain, cardio-respiratory symptoms, and gastrointestinal symptoms.(4) Furthermore, PTSD is independently associated with the inability to return to work 12 months after intensive care unit (ICU) discharge,(5) as well as increased healthcare costs.(6) As such, preventing the development of PTSD could have an enormous influence on long-term patient outcomes as well as public health.

The development of critical illness related PTSD has been linked to patient experience during medical care. Specifically, frightening experiences(7) and acute psychological stress during resuscitation care are strongly associated with the development of PTSD.(8) A central mechanism to the development of PTSD is the process by which traumatic memories are formed.(9) For many patients frightening experiences result in peri-traumatic dissociation, defined as an alteration in time or place with reported feelings of depersonalization, altered perceptions of pain, feeling disconnected, or tunnel vision.(10) This dissociation has been demonstrated to increase the risk for developing PTSD, [10] likely by causing traumatic

information to be encoded in somatosensory, affective, nonlinguistic, and relatively uncontrolled fragmented memories.(11) Our overarching hypothesis is that interventions, which focus on decreasing the degree of acute stress (i.e. frightening experiences) and dissociation during the traumatic event in the hospital, will shift traumatic information processing from developing uncontrollable fragmented memory, to a more controllable and cognitive memory process, and thus prevent or reduce PTSD severity in survivors of critical illness.

The first step towards testing this hypothesis is to collate the world's literature on interventions aimed at preventing or reducing PTSD symptoms in patients who survive medical emergencies. We hypothesize that there are currently few or no interventions aimed at reducing the degree of acute stress and dissociation, during the traumatic event in the hospital, in order to prevent chronic PTSD in this population.

Methods and analysis

Protocol and registration

This systematic review protocol is prepared in accordance with the Cochrane handbook for systematic reviews of interventions,(12) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement.(13) The final results will be reported according to PRISMA and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.(14, 15) This systematic review has been registered in the PROSPERO international prospective register of systematic reviews (registration number CRD42017069672).

Search for and identification of studies

An electronic search will include the following databases: CENTRAL, MEDLINE,

EMBASE, and CINAHL. The search terms include the concepts of post-traumatic stress, critical care, and prevention. These strategies were developed by a group of experts, including a clinical psychologist and intensivists with experience performing systematic reviews. We used a combination of standardized terms and key words, and modeled the search after a previously published systematic review examining the prevalence of ICU related PTSD.(2) The fully reproducible search strategy is provided in the online supplement. In order to identify potentially unpublished data from clinical trials we will search websites containing details on clinical trials registration (National Library of Medicine – ClinicalTrials.gov and the World Health Organization – International Clinical Trials Registry Platform). Registered but unpublished trials will be considered eligible for inclusion if the registration website indicates that enrollment in the clinical trial had been completed. We will also screen reference lists of the articles we select for inclusion to identify additional studies for potential inclusion.

Eligibility criteria

We will include all human prospective interventional trials to prevent PTSD in the critically-ill and injured. In order to be included all studies must contain (1) adult patients diagnosed with a critical illness or injury; (2) patients treated in an emergency department or ICU setting; (3) an intervention arm in which subjects clearly underwent an intervention aimed at preventing or reducing PTSD symptoms, as the single experimental intervention; (4) a clearly defined control arm in which subjects received placebo or standard of care therapy; and (5) an outcome measure assessing development of acute stress or PTSD symptoms. We will consider studies eligible for review regardless of language or publication type. We will exclude studies that are secondary reports of previously published trials. We also will exclude papers that are reviews, correspondence, or editorials; however, we will screen the reference lists of review articles to identify further studies for inclusion.

Study selection and data abstraction

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Assessment of study bias

For each randomized clinical trial, we will assess the quality of the studies selected for inclusion using the Cochrane Collaboration's tool for assessing the risk of bias in clinical trials evaluating six domains (selection, performance, detection, attrition, reporting, and other biases).(12) For each non-randomized clinical trial, we will assess the quality of the studies selected using the Newcastle-Ottawa Quality Assessment Scale, as recommended in the Cochrane Handbook.(12)

Analysis

We will perform a primarily qualitative analysis of the data in accordance with the recommended methodology for qualitative reviews published in the Cochrane Handbook.(12) We will collate and summarize clinical trials in table format, stratified by individual publication. We will table: (1) study type, (2) population sampled (e.g. motor vehicle crash, sepsis patients), (3) description of intervention performed, (4) timing of intervention, (5) outcome measures,

including primary and all secondary outcomes, and (6) effect of intervention on outcome measures compared to control groups.

Given the likely heterogeneity in both interventions and outcome measures it is unlikely that it will be possible to pool data. However, if after conducting the systematic review it is determined data can be pooled, we will perform meta-analyses using random effects models to calculate overall effect sizes and 95% confidence intervals between intervention and control groups. For binary data, such as development of PTSD (yes/no), odds ratios will be calculated, and for continuous outcomes mean differences will be reported. A p value of < 0.05 will be considered statistically significant. Finally, the I^2 statistic will be used to assess heterogeneity between studies. We will consider the following thresholds for the I^2 statistic: low (25-49%), moderate (50-74%), and high (≥75%) values.(16)

Protocol amendments

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Ethics and dissemination

No ethical approval will be required for this systematic review of completed studies. Results from this systematic review will be submitted to peer-reviewed journals for publication, and to national meetings in presentation form. We anticipate that this study will identify a need for further research aimed at developing early interventions to prevent or reduce PTSD symptoms in survivors of critical illness.

Discussion

There has been an increasing understanding that emotional trauma in the form of PTSD is common among patients who experience serious health emergencies and survive critical

illness. PTSD has been shown to have long-lasting effects on physical and emotional well-being,(4) along with increasing healthcare costs.(6) However, it is currently unclear if early interventions can prevent or reduce emotional trauma in patients suffering from health emergencies.

This systematic review will collate the world's literature of early interventions aimed at preventing the development of PTSD in survivors of critical illness. We expect to find that there are currently few or no interventions aimed at reducing the degree of acute stress and dissociation, during the traumatic event in the hospital, in order to prevent chronic PTSD in this population. Specifically, we will identify important knowledge gaps in the literature.

The results of this study will contribute to the understanding of critical illness related PTSD, and help prompt future research aimed at further developing interventions to prevent PTSD symptoms in survivors of critical illness.

References

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16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539-1558.

Author contributions: All authors have made substantial contributions to this paper. BWR supervised all aspects of the study design and takes responsibility for the paper as a whole. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. MBR and BWR developed the search strategy. BWR provided statistical expertise. LG and BWR drafted the manuscript. All authors read and contributed substantially to revision of the final manuscript. All authors approved the manuscript in its final form.

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PRISMA-P 2015 CHECKLIST

	Item No	Protocol Page #
✓	1a	Title page
✓	1b	n/a
✓	2	p. 4
✓	3a	Title page
✓	3b	p. 11
✓	4	n/a
✓	5a	p. 11
✓	5b	p. 11
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✓	6	p. 3-4
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✓	13	p. 5
✓	14	p. 6
✓	15a	p. 6-7
✓	15b	p. 6-7
✓	15c	p. 6-7
✓	15d	p. 6-7
✓	16	n/a
✓	17	n/a