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Initial Use of Supplementary Oxygen For Trauma Patients: A Systematic Review

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ABSTRACT

Objective: This systematic review aimed to identify and describe the evidence for supplementary oxygen for spontaneously breathing trauma patients, and for high (0.60-0.90) versus low (0.30-0.50) inspiratory oxygen fraction (FiO_2) for intubated trauma patients in the initial phase of treatment.

Methods: Several databases were systematically searched in September 2017 for studies fulfilling the following criteria: trauma patients (Population); supplementary oxygen/high FiO_2 (Intervention) versus no supplementary oxygen/low FiO_2 (Control) for spontaneously breathing or intubated trauma patients, respectively, in the initial phase of treatment; mortality, complications, days on mechanical ventilation, and/or length of stay (LOS) in hospital/intensive care unit (ICU) (Outcomes); prospective interventional trials (Study design). Two independent reviewers screened and identified studies and extracted data from included studies.

Results: 6142 citations were screened with an inter-rater reliability (Cohen's Kappa) of 0.88. One interventional trial of intubated trauma patients was included. 68 trauma patients were randomized to receive a FiO_2 of 0.80 (intervention group) or 0.50 (control group) during mechanical ventilation (first six hours). There was no significant difference in hospital or ICU LOS between the groups. No patients died in either group. Another interventional trial, not strictly fulfilling the inclusion criteria, was presented for descriptive purposes. 21 trauma patients were alternately assigned to two types of mechanical ventilation (first 48 hours), both aiming at a FiO_2 of 0.40, but resulted in estimated mean FiO_2s of 0.45 (intervention group) and 0.60 (control group). No difference in days on mechanical ventilation was found. Two patients in the control group died, none in the intervention group. No prospective, interventional trials on spontaneously breathing trauma patients were identified.

Conclusions: Evidence for the use of supplementary oxygen for spontaneously breathing trauma patients is lacking, and the evidence for low versus high FiO_2 for intubated trauma patients is limited.

Protocol registration: PROSPERO (ID no. 42016050552).

STRENGTHS AND LIMITATIONS

Strengths

- The use of predefined PICOS (Population, Intervention, Control, Outcomes, Study design) criteria to assess for study eligibility.
- The use of a wide search string in multiple databases.
- The use of a structured screening and inclusion process as well as data collection and risk of bias assessment by two independent authors.

Limitations

- There is a possibility of missing unpublished studies, which creates a potential publication bias.
- It is possible that we did not identify all relevant studies despite our systematic methodology.

BACKGROUND

Trauma is estimated to be the number one cause of death for persons between 1 and 44 years old [1], and costs related to trauma are a significant economic burden to society [2]. The initial (prehospital and early in-hospital) treatment of trauma patients can be crucial for the subsequent injury outcome, but current management is based on guidelines that are not generally well supported by evidence [1, 3], as research in this setting is difficult to conduct for numerous reasons.

Oxygen is probably the most commonly administered drug both in the prehospital and emergency department setting, and several studies have found supplementary oxygen to be widely used in the prehospital treatment of trauma patients [4-6]. Oxygen is cheap, easily administered, and, at least for shorter time frames, widely believed to be without any risk of harm. Supplementary oxygen treatment is recommended internationally in both the Advanced Trauma Life Support (ATLS) manual and the Pre-Hospital Trauma Life Support (PHTLS) manual [1, 3]. This often leads to a "default" administration of oxygen even without an indication [5]. Supplementary oxygen introduces a risk of inducing hyperoxemia, which has been associated with a greater morbidity and mortality in surgical patients and in patients with acute conditions like stroke, myocardial infarction, and cardiac arrest [7-10].

In intubated patients, an inspiratory oxygen fraction (FiO_2) of 0.30-0.50 is often used during mechanical ventilation. A high FiO_2 (0.60-0.90) intraoperatively has been suggested to reduce the incidence of surgical site infection, however, a recent systematic review did not detect a beneficial effect [10-12].

As the evidence behind the current trauma guidelines with regard to oxygen therapy is not clear, and excessive oxygen administration has been found to be harmful in other patient populations, we sought to perform a systematic review to identify and summarize the evidence for the use of supplementary oxygen for spontaneously breathing trauma patients, and the use of high (0.60-0.90) versus low (0.30-0.50) FiO_2 for intubated trauma patients.

METHODS

Protocol and registration

We conducted a systematic review following the recommendations by the Cochrane Collaboration [13] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [14]. The protocol was completed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [15], and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42016050552) [16].

Eligibility criteria

Inclusion of studies was based on the following predefined PICOS (population, intervention, control, outcomes, study design) criteria: trauma patients > 17 years of age (Population); supplementary oxygen (Intervention) versus no supplementary oxygen (Control) for spontaneously breathing trauma patients and/or high (0.60-0.90) (Intervention) versus low (0.30-0.50) (Control) FiO_2 for intubated trauma patients in the initial phase of treatment (< 24 hours after the traumatic incident including both prehospital and in-hospital phases); all-cause mortality, in-hospital mortality, in-hospital complications, days on mechanical ventilation, and/or length of stay (LOS) in hospital/intensive care unit (ICU) (Outcomes); prospective interventional trials (randomized and non-randomized) (Study design). Observational studies, reviews, expert opinions, case reports, letters, abstracts, and editorials were excluded. There was no restriction to language or year of publication. Potential eligible studies where the full-text could not be found were excluded.

Information sources and search methods

We searched MEDLINE, EMBASE, and the Cochrane Library on September 22nd 2016 using the following predefined search string (presented search strategy is from MEDLINE):

1. ((trauma) OR traumat*) OR traumatic injury
2. (((((oxygen*) OR oxygen) OR oxygenation) OR supplemental oxygen) OR fio2) OR hyperox*
3. (((((((30 day mortality) OR mortal*) OR all cause mortality) OR complicat*) OR in-hospital mortality) OR length of stay) OR LOS) OR hospital mortality[MeSH Terms]) OR mortality[MeSH Terms]

4. #1 AND #2 AND #3
5. Filter: Humans

Modification of the search string was made to fit EMBASE and the Cochrane Library format, respectively. The search was updated on September 3rd 2017, and no new studies were found.

Study selection

Two independent authors (TGE and JSB) screened titles and abstracts from the primary search in all three databases. Screening was performed using Covidence (an online program facilitating the production of systematic reviews developed by the Cochrane Group) [17]. Interrater reliability was calculated using Cohen's Kappa statistics. Both authors evaluated relevant studies in full text independently. Disagreement was resolved by discussion. If agreement could not be reached a senior author (JS or LSR) was involved. Bibliographies of included studies were reviewed for further potentially relevant studies (so-called "snowballing").

Data collection and data items

Data extraction was performed by two authors (TGE, JSB) independently using predetermined forms and facilitated by the data extraction tool in Covidence. Collected study characteristics included study setting and country, study period, and publication year. Data on methods, population, interventions, and outcomes included study design, blinding, aim of the study, inclusion and exclusion criteria, number of included patients, baseline characteristics (i.e. age, gender, mechanism of injury), fraction of inspired oxygen, and oxygenation assessment of the intervention and control group, respectively, as well as any of the predefined outcome measures (primary outcome measure: all-cause mortality at 30 days; secondary outcome measures: in-hospital mortality, in-hospital complications, days on mechanical ventilation, and/or LOS in hospital/ICU).

Risk of bias assessment

The quality of the included studies was assessed by two independent authors (TGE, JSB) using the Cochrane risk of bias assessment tool in Covidence [18], which consists of seven specific domains (random

sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other bias). In each domain the study is judged to have a low, high, or unclear risk of bias.

Summary measures and synthesis of results

This systematic review was expected to be a descriptive summary of the current evidence.

RESULTS

Our combined search strategy identified 6142 records to be considered for inclusion. After screening titles and abstracts, 60 articles were evaluated in full text for eligibility. An interrater reliability (Cohen's Kappa) of 0.88 (confidence interval (CI): 0.82-0.94) for screening and selecting studies was obtained. After full text review, only one study fulfilled the inclusion criteria and was included in the systematic review [19] (Figure 1). Another study, which did not strictly fulfill the inclusion criteria, was also included for descriptive purposes. Both studies were prospective, interventional trials and included intubated trauma patients, and thus no prospective, interventional trials of spontaneously breathing trauma patients were identified. Characteristics, methods, and results for the two included studies are summarized in Table 1.

Taher et al. [19] performed a randomized study of 68 mechanically ventilated adult patients sustaining severe traumatic brain injury (TBI). The patients were randomized to receive a FiO_2 of either 0.80 (intervention group) or 0.50 (control group) during the first six hours of treatment. A total of 34 patients in each group completed the study. The two groups were similar in terms of age, gender distribution, and GCS on admission. Relevant outcomes for this systematic review were LOS in hospital and LOS in ICU. The study found no statistically significant difference between the intervention and control group in either of these outcomes measures (hospital LOS: 11.4 days (SD: 5.4) vs. 13.9 days (SD: 8.1), respectively, p=0.14; ICU LOS: 9.4 days (SD: 6.6) vs. 11.4 days (SD: 8.4), respectively, p=0.28). No patients in either group died.

The study by Barzilay et al. [20] included 21 adult patients with chest trauma and severe respiratory insufficiency due to flail chest or pulmonary contusion requiring mechanical ventilation. Patients were alternately assigned to two different mechanical ventilation strategies: conventional mechanical ventilation or high-frequency positive pressure with low-rate ventilation. FiO_2 was set to be 0.40 in both groups, but subsequently adjusted to arterial oxygen tension and therefore different between the two groups according to the results. Eleven patients in the intervention group received an estimated mean FiO_2 of 0.45 and had a mean arterial oxygen tension (PaO_2) of 89.91 ± 10.24 mmHg during the first 48 hours after hospital admission. The control group consisted of ten similar patients receiving an estimated mean FiO_2 of 0.60 and had a mean PaO_2 of 78.43 ± 11.13 mmHg during the first 48 hours after hospital admission. Neither of these

FiO_2s were reported in detail, but can be estimated from table 3 in the article. No simple relationship was found between the estimated FiO_2 and PaO_2 values presumably as a consequence of the two different ventilation strategies. Outcomes relevant to this systematic review were days on mechanical ventilation and mortality. The study found no statistically significant difference in days on mechanical ventilation between the intervention group and the control group (4.2 days (SD: 0.91) vs. 6.1 days (SD: 0.8), respectively, $p<0.1$). In terms of mortality, two (20%) patients in the control group died compared to none in the intervention group. The p-value was not reported, but the difference was not statistically significant using Fisher's exact test.

The risk of bias assessment for the included studies is presented in Table 2. In the study by Taher et al., three domains were judged to have a low risk of bias (blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data), none to have a high risk of bias, and four domains to have an unclear risk of bias (random sequence generation, allocation concealment, selective reporting, other bias). The study by Barzilay et al. was judged to have two domains with low risk of bias (blinding of participants and personnel, blinding of outcome assessment), two domains with high risk of bias (allocation concealment, other bias), and three domains with an unclear risk of bias (random sequence generation, incomplete outcome data, selective reporting).

DISCUSSION

Summary of evidence

In this systematic review of interventional trials of the use of supplementary oxygen in the initial treatment of trauma patients, we identified no studies of spontaneously breathing patients, and only one interventional trial of intubated trauma patients was found to fulfill the inclusion criteria. Taher et al. [19] found the low FiO_2 group (0.50) to have slightly longer LOS in hospital and LOS in ICU than the high FiO_2 group (0.80), however, these differences were not statistically significant. Additionally, no patients died in either group. In another study by Barzilay et al. [20], which did not strictly fulfill the inclusion criteria, no statistically significant differences were found between the groups, although patients in the high FiO_2 group (0.60) tended to have a higher mortality and more days on mechanical ventilation than the patients in the low FiO_2 group (0.45). Due to the low number as well as heterogeneity of the included studies, we neither found it possible to pool the results of the two studies, nor to draw any conclusions from these findings.

The rationale for supplementation of oxygen for various patient groups has for decades – and even centuries – seemed self-evident for most health-care providers [21]. Oxygen supplementation, often in excess, has been considered a safe measure rather than an intervention that could potentially be harmful and thus needing a clear indication of administration. Supplementation of oxygen has, until recently, escaped the critical evaluation of its value and indication as is necessary for all other drugs not having the same historical, "self-evident" benefit as is the case for oxygen. As previously described, trauma patient management is mostly based on guideline recommendations including rather liberal and non-specific oxygen supplementation. Thus, it seems surprising that, even though supplementary oxygen is widely used in the treatment of trauma patients and included in international trauma guidelines, this systematic review finds that the evidence for the use of supplementary oxygen for spontaneously breathing trauma patients is non-existing, and for mechanically ventilated trauma patients the evidence is extremely limited and of low quality. In an era of evidence-based medicine these findings seem inappropriate, and we cannot continue to avoid investigating the potential benefits and harms of a drug that is so widely used.

Supplementary oxygen increases the partial pressure of oxygen in the alveoli, thus increasing the oxygen gradient across the alveolar-capillary membrane. This is likely to increase the PaO_2 when oxygenation is impeded by a barrier in the transport of oxygen across the alveolar-capillary membrane. However, that is not common in trauma patients. On the other hand, it can be reasonable to administer supplementary oxygen in order to increase the amount of oxygen in the lungs to prolong the safe apnea time [22].

The evidence for the use of supplementary oxygen has been investigated in recently published systematic reviews. In a Cochrane review from 2015 Wetterslev et al. [10] included 28 studies and found no association between perioperative FiO_2 (high: 0.60-0.90 vs. low: 0.30-0.40) and post-operative surgical site infection and mortality. In another Cochrane review of supplementary oxygen for patients with suspected or confirmed acute myocardial infarction (AMI), Cabello et al. [23] included five studies, and they were not able to draw conclusions for or against the use of supplementary oxygen for patients with AMI. Hyperoxia in post-return of spontaneous circulation (ROSC) cardiac arrest (CA) patients has been studied in a systematic review and meta-analysis by Wang et al. [9]. 14 studies were included, and the authors found hyperoxia to be correlated with increased in-hospital mortality in a meta-analysis of eight of the included studies. Finally, Damiani et al. [7] have looked at the association between arterial hyperoxia and mortality for adult ICU patients (mechanically ventilated, post-cardiac arrest, stroke, TBI) in a systematic review and meta-analysis from 2014 of 17 studies. In the meta-analysis hyperoxia was associated with increased mortality for post-cardiac arrest, stroke, and TBI patients, though the authors report the studies to be rather heterogeneous. As the trauma population is a very heterogeneous and typically a younger and less comorbid group of patients than other critically ill populations (i.e. AMI, CA, stroke) the results of the before-mentioned systematic reviews of other patient populations cannot be extrapolated to the trauma population. However, there seems to be an implication that treatment with excess oxygen and hyperoxia can be harmful or at least not beneficial. This, again, stresses the need for investigating the effects of supplementary oxygen and cases of hyperoxia in the trauma population.

Strengths and limitations

This systematic review was conducted in accordance with the PRISMA-guidelines [14] ensuring a systematic and internationally accepted methodological approach. The strengths of this approach include predefined PICOS criteria used to assess for study eligibility, the use of a wide search string in multiple databases, a structured screening and inclusion process by two independent authors, as well as data collection and risk of bias assessment by the same two independent authors using predetermined forms. Our study is limited by the weaknesses of a systematic review in general: The possibility of missing unpublished studies, which creates a potential publication bias, and the possibility that we did not identify all relevant studies despite our systematic methodology. The patient population we included was defined in rather general terms (i.e. adult trauma patients), which may have increased the heterogeneity of the studies, however, we found this to be necessary in order to increase the clinical relevance of our findings. We wanted to study the initial treatment phase of trauma patients, and chose this to be the first 24 hours after the traumatic incident. This time cut-off was chosen rather arbitrarily and did exclude one potentially eligible study [24]. As per our inclusion criteria for this systematic review, we wanted to include both prehospital and in-hospital studies, however, both included studies investigated in-hospital patients with no data on the prehospital supplementary oxygen treatment. As a large proportion of trauma patients receive prehospital supplementary oxygen [5, 6], it is a limitation not to know whether the per protocol FiO_2-group allocation is the only oxygenation treatment the patient has received since the traumatic incident.

The study by Barzilay et al. was included in the review despite lacking strict adherence to the inclusion criteria. We chose to do this, as evidence in this field proved to be extremely sparse, and we wished to report as much of the existing evidence as possible.

We were only able to include two small studies of mechanically ventilated trauma patients, and two different methods of mechanical ventilation were used in the study by Barzilay et al. Thus, the studies were not suitable for pooling results, and we are neither able to draw any conclusions nor provide recommendations for the FiO_2 for mechanically ventilated trauma patients. Furthermore, as no studies of spontaneously breathing trauma patients were found we cannot provide recommendations for the use of supplementary oxygen for spontaneously breathing trauma patients either.

CONCLUSIONS

In this systematic review of supplementary oxygen for trauma patients in the initial phase of treatment, we identified no interventional trials including spontaneously breathing trauma patients and only two small low quality studies assessing oxygen fraction in intubated trauma patients. Thus, the current practice of liberal oxygen administration must be questioned, and interventional studies of supplementary oxygen should be conducted in trauma patients.

FUNDING

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

AUTHOR'S CONTRIBUTIONS

TGE, JSB, JS, and LSR have contributed to conception and design of the study.

TGE and JSB have contributed to the acquisition of data.

TGE, JSB, JS, and LSR have contributed to the analysis and interpretation of data.

TGE, JSB, JS, and LSR have participated in drafting and revising the manuscript critically.

TGE, JSB, JS, and LSR have given their final approval of the manuscript to be submitted.

DATA SHARING STATEMENT

Data sharing is not applicable for this systematic review.

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FIGURES

Figure 1

Figure legends: PRISMA flow diagram of the identification, screening, eligibility, and inclusion process [14]. *One of the included studies [20] did not strictly meet the inclusion criteria, however, it is included for descriptive purposes.

Table 1: Characteristics, methods, and results for the included studies of supplementary oxygen for trauma patients.

	Taher et al. [19]		Bazilay et al. [20]*	
Study characteristics				
Setting	Emergency ward		General ICU	
Period	2014		January 1981 – January 1984	
Geographical location	Hamadan, Iran		Afula, Israel	
Methods				
Aim	*"… to assess the effects of normobaric hyperoxia on clinical neurological outcomes of patients with severe TBIs."*		*"… compare the results using ventilatory method, which combines HFPPV [high-frequency positive-pressure ventilation] and low-rate conventional mechanical ventilation (LRCMV), to the results using conventional mechanical ventilation (CMV) with PEEP."*	
Blinding	Double blinded		Not reported	
Study design	Randomized controlled trial		Interventional, non-randomized	
Inclusion criteria	Age 18-65 years; <6 hours passed since the accident; hemodynamic stability; GCS 3-8		All patients admitted to the ICU with a diagnosis of severe respiratory insufficiency due to flail chest or pulmonary contusion	
Exclusion criteria	Pregnancy; chronic disease such as diabetes mellitus, ischemic heart disease, renal failure, acute pulmonary edema, history of massive myocardial infarction, and heart failure; blood pressure <90/60 mmHg; successful CPR; death or loss to follow-up; patients in the control group in which oxygen therapy was inevitable		Not reported	
	Intervention group	**Control group**	**Intervention group**	**Control group**
Results				
No. of patients	34	34	11	10
Age [years], mean (SD)	39.7 (14.1)	45.7 (13.3)	40.6 (22.45)	39.8 (18.18)
Female sex, no. (%)	9 (26.5)	11 (32.4)	Not reported	Not reported
GCS on admission, mean (SD)	7.4 (0.79)	7.4 (0.89)		
FiO_2, mean (SD)	0.80	0.50	0.45†	0.60†
PaO_2 [mmHg], mean (SD)	Not reported	Not reported	89.91 +/- 10.24†	78.43 +/- 11.13†
Outcome measures				
30 day all-cause mortality, n (%)	0 (0%)	0 (0%)	0 (0%)	2 (20%)
Hospital LOS [days]	11.4 (5.4)	13.9 (8.1)	Not reported	Not reported
ICU LOS [days]	9.4 (6.6)	11.4 (8.4)	Not reported	Not reported
Days on mechanical ventilation, mean (SD)	Not reported	Not reported	4.2 (0.91)	6.1 (0.8)

*This study did not strictly meet the inclusion criteria, however, it was included for descriptive purposes.

†during first 48 hours in hospital (FiO_2 estimated from other results)

Intensive Care Unit (ICU); Positive end expiratory pressure (PEEP); Traumatic brain injury (TBI); Glasgow Coma Scale Score (GCS); Cardio pulmonary resuscitation (CPR); Standard deviation (SD); inspiratory oxygen fraction (FiO_2); arterial oxygen tension (PaO_2); Length of stay (LOS)

Table 2: Risk of bias assessment for the two included studies.

	Taher et al. [19]		Barzilay et al. [20]*	
Risk of bias domain	**Judgment**	**Support for judgment**	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Unclear	*Quote*: … patients were divided in two groups… ” *Comment*: Not a random component in the sequence generation process.	Unclear	*Comment*: No description of a random component in the sequence generation process.
Allocation concealment (selection bias)	Unclear	*Comment*: No description of allocation concealment.	High	*Quote*: “Patients were assigned alternately to two groups ” *Comment*: Investigators had the possibility of foreseeing the assignment.
Blinding of participants and personnel (performance bias)	Low	Quote: “In this double blind clinical trial… ” Comment: Probably done.	Low	*Comment*: No blinding is described, but the relevant outcomes are not likely to be influences by lack of blinding.
Blinding of outcome assessment (detection bias)	Low	*Comment*: No blinding of outcome assessment is described, but the relevant outcomes are not likely to be influences by lack of blinding.	Low	*Comment*: No blinding of outcome assessment is described, but the relevant outcomes are not likely to be influences by lack of blinding.
Incomplete outcome data (attrition bias)	Low	*Comment*: Outcome is reported for all included patients.	Unclear	*Comment*: The outcomes are not described as being defined before commencing the study.
Selective reporting (reporting bias)	Unclear	*Comment*: No protocol is available and the reported outcomes are not pre-specified in the methods section.	Unclear	*Comment*: As outcomes are not described as being defined before commencing the study, there is insufficient information to assess this domain.
Other bias	Unclear	*Comment*: There is insufficient information on the study design to assess whether an important risk of bias exists.	High	Quote: “Those in the study group were connected to a two-ventilator HFPPV system of our own design” Comment: The authors are likely to have a preference for their own design.

*This study did not strictly meet the inclusion criteria, however, it was included for descriptive purposes.

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PRISMA flow diagram of the identification, screening, eligibility, and inclusion process [14]. *One of the included studies [20] did not strictly meet the inclusion criteria, however, it is included for descriptive purposes.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Initial Use of Supplementary Oxygen For Trauma Patients: A Systematic Review

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Initial Use of Supplementary Oxygen For Trauma Patients: A Systematic Review

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ABSTRACT

Objective: This systematic review aimed to identify and describe the evidence for supplementary oxygen for spontaneously breathing trauma patients, and for high (0.60-0.90) versus low (0.30-0.50) inspiratory oxygen fraction (FiO_2) for intubated trauma patients in the initial phase of treatment.

Methods: Several databases were systematically searched in September 2017 for studies fulfilling the following criteria: trauma patients (Population); supplementary oxygen/high FiO_2 (Intervention) versus no supplementary oxygen/low FiO_2 (Control) for spontaneously breathing or intubated trauma patients, respectively, in the initial phase of treatment; mortality, complications, days on mechanical ventilation, and/or length of stay (LOS) in hospital/intensive care unit (ICU) (Outcomes); prospective interventional trials (Study design). Two independent reviewers screened and identified studies and extracted data from included studies.

Results: 6142 citations were screened with an inter-rater reliability (Cohen's Kappa) of 0.88. One interventional trial of intubated trauma patients was included. 68 trauma patients were randomized to receive a FiO_2 of 0.80 (intervention group) or 0.50 (control group) during mechanical ventilation (first six hours). There was no significant difference in hospital or ICU LOS between the groups. No patients died in either group. Another interventional trial, not strictly fulfilling the inclusion criteria, was presented for descriptive purposes. 21 trauma patients were alternately assigned to two types of mechanical ventilation (first 48 hours), both aiming at a FiO_2 of 0.40, but resulted in estimated mean FiO_2s of 0.45 (intervention group) and 0.60 (control group). No difference in days on mechanical ventilation was found. Two patients in the control group died, none in the intervention group. No prospective, interventional trials on spontaneously breathing trauma patients were identified.

Conclusions: Evidence for the use of supplementary oxygen for spontaneously breathing trauma patients is lacking, and the evidence for low versus high FiO_2 for intubated trauma patients is limited.

Protocol registration: PROSPERO (ID no. 42016050552).

STRENGTHS AND LIMITATIONS

Strengths

- The use of predefined PICOS (Population, Intervention, Control, Outcomes, Study design) criteria to assess for study eligibility.
- The use of a wide search string in multiple databases.
- The use of a structured screening and inclusion process as well as data collection and risk of bias assessment by two independent authors.

Limitations

- There is a possibility of missing unpublished studies, which creates a potential publication bias.
- It is possible that we did not identify all relevant studies despite our systematic methodology.

BACKGROUND

Trauma is estimated to be the number one cause of death for persons between 1 and 44 years old [1], and costs related to trauma are a significant economic burden to society [2]. The initial (prehospital and early in-hospital) treatment of trauma patients can be crucial for the subsequent injury outcome, but current management is based on guidelines that are not generally well supported by evidence [1, 3], as research in this setting is difficult to conduct for numerous reasons.

Oxygen is probably the most commonly administered drug both in the prehospital and emergency department setting, and several studies have found supplementary oxygen to be widely used in the prehospital treatment of trauma patients [4-6]. Oxygen is cheap, easily administered, and, at least for shorter time frames, widely believed to be without any risk of harm. Supplementary oxygen treatment is recommended internationally in both the Advanced Trauma Life Support (ATLS) manual and the Pre-Hospital Trauma Life Support (PHTLS) manual [1, 3]. This often leads to a "default" administration of oxygen even without an indication [5]. Supplementary oxygen treatment is provided to prevent or correct hypoxemia, as this is may cause tissue hypoxia with organ injury. However, supplementary oxygen introduces a risk of hyperoxemia, which is associated with a risk of complications, especially lung damage, and liberal use of oxygen is associated with greater morbidity and mortality in surgical patients and in patients with acute conditions like stroke, myocardial infarction, and cardiac arrest [7-10].

In intubated patients, an inspiratory oxygen fraction (FiO_2) of 0.30-0.50 is often used during mechanical ventilation. A high FiO_2 (0.60-0.90) intraoperatively has been suggested to reduce the incidence of surgical site infection, however, a recent systematic review did not detect a beneficial effect [10-12].

As the evidence behind the current trauma guidelines with regard to oxygen therapy is not clear, and excessive oxygen administration has been found to be harmful in other patient populations, we sought to perform a systematic review to identify and summarize the evidence for the use of supplementary oxygen for spontaneously breathing trauma patients, and the use of high (0.60-0.90) versus low (0.30-0.50) FiO_2 for intubated trauma patients.

METHODS

Protocol and registration

We conducted a systematic review following the recommendations by the Cochrane Collaboration [13] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [14]. The protocol was completed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [15], and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42016050552) [16].

Eligibility criteria

Inclusion of studies was based on the following predefined PICOS (population, intervention, control, outcomes, study design) criteria: trauma patients > 17 years of age (Population); supplementary oxygen (Intervention) versus no supplementary oxygen (Control) for spontaneously breathing trauma patients and/or high (0.60-0.90) (Intervention) versus low (0.30-0.50) (Control) FiO_2 for intubated trauma patients in the initial phase of treatment (< 24 hours after the traumatic incident including both prehospital and in-hospital phases); all-cause mortality, in-hospital mortality, in-hospital complications, days on mechanical ventilation, and/or length of stay (LOS) in hospital/intensive care unit (ICU) (Outcomes); prospective interventional trials (randomized and non-randomized) (Study design). Observational studies, reviews, expert opinions, case reports, letters, abstracts, and editorials were excluded. There was no restriction to language or year of publication. Potential eligible studies where the full-text could not be found were excluded.

Information sources and search methods

We searched MEDLINE, EMBASE, and the Cochrane Library from inception to September 22nd 2016 using the following predefined search string (presented search strategy is from MEDLINE):

1. ((trauma) OR traumat*) OR traumatic injury
2. (((((oxygen*) OR oxygen) OR oxygenation) OR supplemental oxygen) OR fio2) OR hyperox*
3. (((((((30 day mortality) OR mortal*) OR all cause mortality) OR complicat*) OR in-hospital mortality) OR length of stay) OR LOS) OR hospital mortality[MeSH Terms]) OR mortality[MeSH Terms]

4. #1 AND #2 AND #3
5. Filter: Humans

Modification of the search string was made to fit EMBASE and the Cochrane Library format, respectively. The search was updated on September 3rd 2017, and no new studies were found.

Study selection

Two independent authors (TGE and JSB) screened titles and abstracts from the primary search in all three databases. Screening was performed using Covidence (an online program facilitating the production of systematic reviews developed by the Cochrane Group) [17]. Interrater reliability was calculated using Cohen's Kappa statistics. Both authors evaluated relevant studies in full text independently. Disagreement was resolved by discussion. If agreement could not be reached a senior author (JS or LSR) was involved. Bibliographies of included studies were reviewed for further potentially relevant studies (so-called "snowballing").

Data collection and data items

Data extraction was performed by two authors (TGE, JSB) independently using predetermined forms and facilitated by the data extraction tool in Covidence. Collected study characteristics included study setting and country, study period, and publication year. Data on methods, population, interventions, and outcomes included study design, blinding, aim of the study, inclusion and exclusion criteria, number of included patients, baseline characteristics (i.e. age, gender, mechanism of injury), fraction of inspired oxygen, and oxygenation assessment of the intervention and control group, respectively, as well as any of the predefined outcome measures (primary outcome measure: all-cause mortality at 30 days; secondary outcome measures: in-hospital mortality, in-hospital complications, days on mechanical ventilation, and/or LOS in hospital/ICU).

Risk of bias assessment

The quality of the included studies was assessed by two independent authors (TGE, JSB) using the Cochrane risk of bias assessment tool in Covidence [18], which consists of seven specific domains (random

sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other bias). In each domain the study is judged to have a low, high, or unclear risk of bias.

Summary measures and synthesis of results

This systematic review was expected to be a descriptive summary of the current evidence.

RESULTS

Our combined search strategy identified 6142 records to be considered for inclusion. After screening titles and abstracts, 60 articles were evaluated in full text for eligibility. An interrater reliability (Cohen's Kappa) of 0.88 (confidence interval (CI): 0.82-0.94) for screening and selecting studies was obtained. After full text review, only one study fulfilled the inclusion criteria and was included in the systematic review [19] (Figure 1). Another study, which did not strictly fulfill the inclusion criteria, was also included for descriptive purposes. Both studies were prospective, interventional trials and included intubated trauma patients, and thus no prospective, interventional trials of spontaneously breathing trauma patients were identified. Characteristics, methods, and results for the two included studies are summarized in Table 1.

Taher et al. [19] performed a randomized study of 68 mechanically ventilated adult patients sustaining severe traumatic brain injury (TBI). The patients were randomized to receive a FiO_2 of either 0.80 (intervention group) or 0.50 (control group) during the first six hours of treatment. A total of 34 patients in each group completed the study. The two groups were similar in terms of age, gender distribution, and GCS on admission. Relevant outcomes for this systematic review were LOS in hospital and LOS in ICU. The study found no statistically significant difference between the intervention and control group in either of these outcomes measures (hospital LOS: 11.4 days (SD: 5.4) vs. 13.9 days (SD: 8.1), respectively, p=0.14; ICU LOS: 9.4 days (SD: 6.6) vs. 11.4 days (SD: 8.4), respectively, p=0.28). No patients in either group died.

The study by Barzilay et al. [20] included 21 adult patients with chest trauma and severe respiratory insufficiency due to flail chest or pulmonary contusion requiring mechanical ventilation. Patients were alternately assigned to two different mechanical ventilation strategies: conventional mechanical ventilation or high-frequency positive pressure with low-rate ventilation. FiO_2 was set to be 0.40 in both groups, but subsequently adjusted to arterial oxygen tension and therefore different between the two groups according to the results. Eleven patients in the intervention group received an estimated mean FiO_2 of 0.45 and had a mean arterial oxygen tension (PaO_2) of 89.91 ± 10.24 mmHg during the first 48 hours after hospital admission. The control group consisted of ten similar patients receiving an estimated mean FiO_2 of 0.60 and had a mean PaO_2 of 78.43 ± 11.13 mmHg during the first 48 hours after hospital admission. Neither of these

FiO_2s were reported in detail, but can be estimated from the data provided in the article. No simple relationship was found between the estimated FiO_2 and PaO_2 values presumably as a consequence of the two different ventilation strategies. Outcomes relevant to this systematic review were days on mechanical ventilation and mortality. The study found no statistically significant difference in days on mechanical ventilation between the intervention group and the control group (4.2 days (SD: 0.91) vs. 6.1 days (SD: 0.8), respectively, $p<0.1$). In terms of mortality, two (20%) patients in the control group died compared to none in the intervention group. The p-value was not reported, but the difference was not statistically significant using Fisher's exact test.

The risk of bias assessment for the included studies is presented in Table 2. In the study by Taher et al., three domains were judged to have a low risk of bias (blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data), none to have a high risk of bias, and four domains to have an unclear risk of bias (random sequence generation, allocation concealment, selective reporting, other bias). The study by Barzilay et al. was judged to have two domains with low risk of bias (blinding of participants and personnel, blinding of outcome assessment), two domains with high risk of bias (allocation concealment, other bias), and three domains with an unclear risk of bias (random sequence generation, incomplete outcome data, selective reporting).

DISCUSSION

Summary of evidence

In this systematic review of interventional trials of the use of supplementary oxygen in the initial treatment of trauma patients, we identified no studies of spontaneously breathing patients, and only one interventional trial of intubated trauma patients was found to fulfill the inclusion criteria. Taher et al. [19] found the low FiO_2 group (0.50) to have slightly longer LOS in hospital and LOS in ICU than the high FiO_2 group (0.80), however, these differences were not statistically significant. Additionally, no patients died in either group. In another study by Barzilay et al. [20], which did not strictly fulfill the inclusion criteria, no statistically significant differences were found between the groups, although patients in the high FiO_2 group (0.60) tended to have a higher mortality and more days on mechanical ventilation than the patients in the low FiO_2 group (0.45). Due to the low number as well as heterogeneity of the included studies, we neither found it possible to pool the results of the two studies, nor to draw any conclusions from these findings.

The rationale for supplementation of oxygen for various patient groups has for decades – and even centuries – seemed self-evident for most health-care providers [21]. Oxygen supplementation, often in excess, has been considered a safe measure rather than an intervention that could potentially be harmful and thus needing a clear indication of administration. Supplementation of oxygen has, until recently, escaped the critical evaluation of its value and indication as is necessary for all other drugs not having the same historical, "self-evident" benefit as is the case for oxygen. As previously described, trauma patient management is mostly based on guideline recommendations including rather liberal and non-specific oxygen supplementation. Thus, it seems surprising that, even though supplementary oxygen is widely used in the treatment of trauma patients and included in international trauma guidelines, this systematic review finds that the evidence for the use of supplementary oxygen for spontaneously breathing trauma patients is non-existing, and for mechanically ventilated trauma patients the evidence is extremely limited and of low quality. In an era of evidence-based medicine these findings seem inappropriate, and we cannot continue to avoid investigating the potential benefits and harms of a drug that is so widely used.

Supplementary oxygen increases the partial pressure of oxygen in the alveoli, thus increasing the oxygen gradient across the alveolar-capillary membrane. This is likely to increase the PaO_2 when oxygenation is impeded by a barrier in the transport of oxygen across the alveolar-capillary membrane. However, that is not common in trauma patients. On the other hand, it can be reasonable to administer supplementary oxygen in order to increase the amount of oxygen in the lungs to prolong the safe apnea time [22].

Both hypoxemia and hyperoxemia may be harmful. Hypoxemia may cause hypoxic neuronal cell death leading to irreversible brain damage, whereas hyperoxemia has been found to increase the risk of pulmonary complications like the formation of atelectases and airway inflammation [23].

The evidence for the use of supplementary oxygen has been investigated in recently published systematic reviews. In a Cochrane review from 2015 Wetterslev et al. [10] included 28 studies and found no association between perioperative FiO_2 (high: 0.60-0.90 vs. low: 0.30-0.40) and post-operative surgical site infection and mortality. In another Cochrane review of supplementary oxygen for patients with suspected or confirmed acute myocardial infarction (AMI), Cabello et al. [24] included five studies, and they were not able to draw conclusions for or against the use of supplementary oxygen for patients with AMI. Hyperoxia in post-return of spontaneous circulation (ROSC) cardiac arrest (CA) patients has been studied in a systematic review and meta-analysis by Wang et al. [9]. 14 studies were included, and the authors found hyperoxia to be correlated with increased in-hospital mortality in a meta-analysis of eight of the included studies. Finally, Damiani et al. [7] have looked at the association between arterial hyperoxia and mortality for adult ICU patients (mechanically ventilated, post-cardiac arrest, stroke, TBI) in a systematic review and meta-analysis from 2014 of 17 studies. In the meta-analysis hyperoxia was associated with increased mortality for post-cardiac arrest, stroke, and TBI patients, though the authors report the studies to be rather heterogeneous. As the trauma population is a very heterogeneous and typically a younger and less comorbid group of patients than other critically ill populations (i.e. AMI, CA, stroke) the results of the before-mentioned systematic reviews of other patient populations cannot be extrapolated to the trauma population. However, there seems to be an implication that treatment with excess oxygen and hyperoxia can be harmful or at least not beneficial. This, again, stresses the need for investigating the effects of supplementary oxygen and cases of hyperoxia in the trauma population.

Strengths and limitations

This systematic review was conducted in accordance with the PRISMA-guidelines [14] ensuring a systematic and internationally accepted methodological approach. The strengths of this approach include predefined PICOS criteria used to assess for study eligibility, the use of a wide search string in multiple databases, a structured screening and inclusion process by two independent authors, as well as data collection and risk of bias assessment by the same two independent authors using predetermined forms. Our study is limited by the weaknesses of a systematic review in general: The possibility of missing unpublished studies, which creates a potential publication bias, and the possibility that we did not identify all relevant studies despite our systematic methodology. The patient population we included was defined in rather general terms (i.e. adult trauma patients), which may have increased the heterogeneity of the studies, however, we found this to be necessary in order to increase the clinical relevance of our findings. We wanted to study the initial treatment phase of trauma patients, and chose this to be the first 24 hours after the traumatic incident. This time cut-off was chosen rather arbitrarily and did exclude one potentially eligible study [25]. As per our inclusion criteria for this systematic review, we wanted to include both prehospital and in-hospital studies, however, both included studies investigated in-hospital patients with no data on the prehospital supplementary oxygen treatment. As a large proportion of trauma patients receive prehospital supplementary oxygen [5, 6], it is a limitation not to know whether the per protocol FiO_2-group allocation is the only oxygenation treatment the patient has received since the traumatic incident.

The study by Barzilay et al. was included in the review despite lacking strict adherence to the inclusion criteria. We chose to do this, as evidence in this field proved to be extremely sparse, and we wished to report as much of the existing evidence as possible.

We were only able to include two small studies of mechanically ventilated trauma patients, and two different methods of mechanical ventilation were used in the study by Barzilay et al. Thus, the studies were not suitable for pooling results, and we are neither able to draw any conclusions nor provide recommendations for the FiO_2 for mechanically ventilated trauma patients. Furthermore, as no studies of spontaneously breathing trauma patients were found we cannot provide recommendations for the use of supplementary oxygen for spontaneously breathing trauma patients either.

CONCLUSIONS

In this systematic review of supplementary oxygen for trauma patients in the initial phase of treatment, we identified no interventional trials including spontaneously breathing trauma patients and only two small low quality studies assessing oxygen fraction in intubated trauma patients. Thus, the current practice of liberal oxygen administration must be questioned, and interventional studies of supplementary oxygen should be conducted in trauma patients.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

AUTHOR'S CONTRIBUTIONS

TGE, JSB, JS, and LSR have contributed to conception and design of the study.

TGE and JSB have contributed to the acquisition of data.

TGE, JSB, JS, and LSR have contributed to the analysis and interpretation of data.

TGE, JSB, JS, and LSR have participated in drafting and revising the manuscript critically.

TGE, JSB, JS, and LSR have given their final approval of the manuscript to be submitted.

DATA SHARING STATEMENT

Data sharing is not applicable for this systematic review.

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FIGURES

Figure 1

Figure legends: PRISMA flow diagram of the identification, screening, eligibility, and inclusion process [14]. *One of the included studies [20] did not strictly meet the inclusion criteria, however, it is included for descriptive purposes.

Table 1: Characteristics, methods, and results for the included studies of supplementary oxygen for trauma patients.

	Taher et al. [19]		Bazilay et al. [20]*	
Study characteristics				
Setting	Emergency ward		General ICU	
Period	2014		January 1981 – January 1984	
Geographical location	Hamadan, Iran		Afula, Israel	
Methods				
Aim	*"… to assess the effects of normobaric hyperoxia on clinical neurological outcomes of patients with severe TBIs."*		*"… compare the results using ventilatory method, which combines HFPPV [high-frequency positive-pressure ventilation] and low-rate conventional mechanical ventilation (LRCMV), to the results using conventional mechanical ventilation (CMV) with PEEP."*	
Blinding	Double blinded		Not reported	
Study design	Randomized controlled trial		Interventional, non-randomized	
Inclusion criteria	Age 18-65 years; <6 hours passed since the accident; hemodynamic stability; GCS 3-8		All patients admitted to the ICU with a diagnosis of severe respiratory insufficiency due to flail chest or pulmonary contusion	
Exclusion criteria	Pregnancy; chronic disease such as diabetes mellitus, ischemic heart disease, renal failure, acute pulmonary edema, history of massive myocardial infarction, and heart failure; blood pressure <90/60 mmHg; successful CPR; death or loss to follow-up; patients in the control group in which oxygen therapy was inevitable		Not reported	
	Intervention group	**Control group**	**Intervention group**	**Control group**
Results				
No. of patients	34	34	11	10
Age [years], mean (SD)	39.7 (14.1)	45.7 (13.3)	40.6 (22.45)	39.8 (18.18)
Female sex, no. (%)	9 (26.5)	11 (32.4)	Not reported	Not reported
GCS on admission, mean (SD)	7.4 (0.79)	7.4 (0.89)		
FiO_2, mean (SD)	0.80	0.50	0.45†	0.60†
PaO_2 [mmHg], mean (SD)	Not reported	Not reported	89.91 +/- 10.24†	78.43 +/- 11.13†
Outcome measures				
30 day all-cause mortality, n (%)	0 (0%)	0 (0%)	0 (0%)	2 (20%)
Hospital LOS [days]	11.4 (5.4)	13.9 (8.1)	Not reported	Not reported
ICU LOS [days]	9.4 (6.6)	11.4 (8.4)	Not reported	Not reported
Days on mechanical ventilation, mean (SD)	Not reported	Not reported	4.2 (0.91)	6.1 (0.8)

*This study did not strictly meet the inclusion criteria, however, it was included for descriptive purposes.

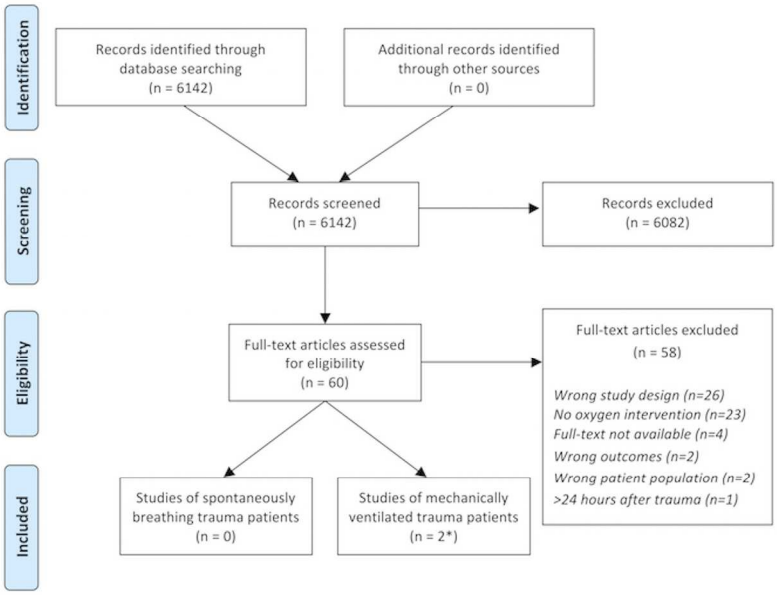
†during first 48 hours in hospital (FiO_2 estimated from other results)

Intensive Care Unit (ICU); Positive end expiratory pressure (PEEP); Traumatic brain injury (TBI); Glasgow Coma Scale Score (GCS); Cardio pulmonary resuscitation (CPR); Standard deviation (SD); inspiratory oxygen fraction (FiO_2); arterial oxygen tension (PaO_2); Length of stay (LOS)

Table 2: Risk of bias assessment for the two included studies.

	Taher et al. [19]		Barzilay et al. [20]*	
Risk of bias domain	**Judgment**	**Support for judgment**	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Unclear	*Quote*: … patients were divided in two groups… ” *Comment*: Not a random component in the sequence generation process.	Unclear	*Comment*: No description of a random component in the sequence generation process.
Allocation concealment (selection bias)	Unclear	*Comment*: No description of allocation concealment.	High	*Quote*: “Patients were assigned alternately to two groups ” *Comment*: Investigators had the possibility of foreseeing the assignment.
Blinding of participants and personnel (performance bias)	Low	Quote: “In this double blind clinical trial… ” Comment: Probably done.	Low	*Comment*: No blinding is described, but the relevant outcomes are not likely to be influences by lack of blinding.
Blinding of outcome assessment (detection bias)	Low	*Comment*: No blinding of outcome assessment is described, but the relevant outcomes are not likely to be influences by lack of blinding.	Low	*Comment*: No blinding of outcome assessment is described, but the relevant outcomes are not likely to be influences by lack of blinding.
Incomplete outcome data (attrition bias)	Low	*Comment*: Outcome is reported for all included patients.	Unclear	*Comment*: The outcomes are not described as being defined before commencing the study.
Selective reporting (reporting bias)	Unclear	*Comment*: No protocol is available and the reported outcomes are not pre-specified in the methods section.	Unclear	*Comment*: As outcomes are not described as being defined before commencing the study, there is insufficient information to assess this domain.
Other bias	Unclear	*Comment*: There is insufficient information on the study design to assess whether an important risk of bias exists.	High	Quote: “Those in the study group were connected to a two-ventilator HFPPV system of our own design” Comment: The authors are likely to have a preference for their own design.

*This study did not strictly meet the inclusion criteria, however, it was included for descriptive purposes.



PRISMA flow diagram of the identification, screening, eligibility, and inclusion process [14]. *One of the included studies [20] did not strictly meet the inclusion criteria, however, it is included for descriptive purposes.

107x152mm (600 x 600 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Initial Use of Supplementary Oxygen For Trauma Patients: A Systematic Review

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Initial Use of Supplementary Oxygen For Trauma Patients: A Systematic Review

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ABSTRACT

Objective: This systematic review aimed to identify and describe the evidence for supplementary oxygen for spontaneously breathing trauma patients, and for high (0.60-0.90) versus low (0.30-0.50) inspiratory oxygen fraction (FiO_2) for intubated trauma patients in the initial phase of treatment.

Methods: Several databases were systematically searched in September 2017 for studies fulfilling the following criteria: trauma patients (Population); supplementary oxygen/high FiO_2 (Intervention) versus no supplementary oxygen/low FiO_2 (Control) for spontaneously breathing or intubated trauma patients, respectively, in the initial phase of treatment; mortality, complications, days on mechanical ventilation, and/or length of stay (LOS) in hospital/intensive care unit (ICU) (Outcomes); prospective interventional trials (Study design). Two independent reviewers screened and identified studies and extracted data from included studies.

Results: 6142 citations were screened with an inter-rater reliability (Cohen's Kappa) of 0.88. One interventional trial of intubated trauma patients was included. 68 trauma patients were randomized to receive a FiO_2 of 0.80 (intervention group) or 0.50 (control group) during mechanical ventilation (first six hours). There was no significant difference in hospital or ICU LOS between the groups. No patients died in either group. Another interventional trial, not strictly fulfilling the inclusion criteria, was presented for descriptive purposes. 21 trauma patients were alternately assigned to two types of mechanical ventilation (first 48 hours), both aiming at a FiO_2 of 0.40, but resulted in estimated mean FiO_2s of 0.45 (intervention group) and 0.60 (control group). No difference in days on mechanical ventilation was found. Two patients in the control group died, none in the intervention group. No prospective, interventional trials on spontaneously breathing trauma patients were identified.

Conclusions: Evidence for the use of supplementary oxygen for spontaneously breathing trauma patients is lacking, and the evidence for low versus high FiO_2 for intubated trauma patients is limited.

Protocol registration: PROSPERO (ID no. 42016050552).

STRENGTHS AND LIMITATIONS

Strengths

- The use of predefined PICOS (Population, Intervention, Control, Outcomes, Study design) criteria to assess for study eligibility.
- The use of a wide search string in multiple databases.
- The use of a structured screening and inclusion process as well as data collection and risk of bias assessment by two independent authors.

Limitations

- There is a possibility of missing unpublished studies, which creates a potential publication bias.
- It is possible that we did not identify all relevant studies despite our systematic methodology.

BACKGROUND

Trauma is estimated to be the number one cause of death for persons between 1 and 44 years old [1], and costs related to trauma are a significant economic burden to society [2]. The initial (prehospital and early in-hospital) treatment of trauma patients can be crucial for the subsequent injury outcome, but current management is based on guidelines that are not generally well supported by evidence [1, 3], as research in this setting is difficult to conduct for numerous reasons.

Oxygen is probably the most commonly administered drug both in the prehospital and emergency department setting, and several studies have found supplementary oxygen to be widely used in the prehospital treatment of trauma patients [4-6]. Oxygen is cheap, easily administered, and, at least for shorter time frames, widely believed to be without any risk of harm. Supplementary oxygen treatment is recommended internationally in both the Advanced Trauma Life Support (ATLS) manual and the Pre-Hospital Trauma Life Support (PHTLS) manual [1, 3]. This often leads to a "default" administration of oxygen even without an indication [5]. Supplementary oxygen treatment is provided to prevent or correct hypoxemia, as this is may cause tissue hypoxia with organ injury. However, supplementary oxygen introduces a risk of hyperoxemia, which is associated with a risk of complications, especially lung damage, and liberal use of oxygen is associated with greater morbidity and mortality in surgical patients and in patients with acute conditions like stroke, myocardial infarction, and cardiac arrest [7-10].

In intubated patients, an inspiratory oxygen fraction (FiO_2) of 0.30-0.50 is often used during mechanical ventilation. A high FiO_2 (0.60-0.90) intraoperatively has been suggested to reduce the incidence of surgical site infection, however, a recent systematic review did not detect a beneficial effect [10-12].

As the evidence behind the current trauma guidelines with regard to oxygen therapy is not clear, and excessive oxygen administration has been found to be harmful in other patient populations, we sought to perform a systematic review to identify and summarize the evidence for the use of supplementary oxygen for spontaneously breathing trauma patients, and the use of high (0.60-0.90) versus low (0.30-0.50) FiO_2 for intubated trauma patients.

METHODS

Protocol and registration

We conducted a systematic review following the recommendations by the Cochrane Collaboration [13] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [14]. The protocol was completed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [15], and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42016050552) [16].

Eligibility criteria

Inclusion of studies was based on the following predefined PICOS (population, intervention, control, outcomes, study design) criteria: trauma patients > 17 years of age (Population); supplementary oxygen (Intervention) versus no supplementary oxygen (Control) for spontaneously breathing trauma patients and/or high (0.60-0.90) (Intervention) versus low (0.30-0.50) (Control) FiO_2 for intubated trauma patients in the initial phase of treatment (< 24 hours after the traumatic incident including both prehospital and in-hospital phases); all-cause mortality, in-hospital mortality, in-hospital complications, days on mechanical ventilation, and/or length of stay (LOS) in hospital/intensive care unit (ICU) (Outcomes); prospective interventional trials (randomized and non-randomized) (Study design). Observational studies, reviews, expert opinions, case reports, letters, abstracts, and editorials were excluded. There was no restriction to language or year of publication. Potential eligible studies where the full-text could not be found were excluded.

Information sources and search methods

We searched MEDLINE, EMBASE, and the Cochrane Library from inception to September 22nd 2016 using the following predefined search string (presented search strategy is from MEDLINE):

1. ((trauma) OR traumat*) OR traumatic injury
2. (((((oxygen*) OR oxygen) OR oxygenation) OR supplemental oxygen) OR fio2) OR hyperox*
3. (((((((30 day mortality) OR mortal*) OR all cause mortality) OR complicat*) OR in-hospital mortality) OR length of stay) OR LOS) OR hospital mortality[MeSH Terms]) OR mortality[MeSH Terms]

4. #1 AND #2 AND #3
5. Filter: Humans

Modification of the search string was made to fit EMBASE and the Cochrane Library format, respectively. The search was updated on September 3rd 2017, and no new studies were found.

Study selection

Two independent authors (TGE and JSB) screened titles and abstracts from the primary search in all three databases. Screening was performed using Covidence (an online program facilitating the production of systematic reviews developed by the Cochrane Group) [17]. Interrater reliability was calculated using Cohen's Kappa statistics. Both authors evaluated relevant studies in full text independently. Disagreement was resolved by discussion. If agreement could not be reached a senior author (JS or LSR) was involved. Bibliographies of included studies were reviewed for further potentially relevant studies (so-called "snowballing").

Data collection and data items

Data extraction was performed by two authors (TGE, JSB) independently using predetermined forms and facilitated by the data extraction tool in Covidence. Collected study characteristics included study setting and country, study period, and publication year. Data on methods, population, interventions, and outcomes included study design, blinding, aim of the study, inclusion and exclusion criteria, number of included patients, baseline characteristics (i.e. age, gender, mechanism of injury), fraction of inspired oxygen, and oxygenation assessment of the intervention and control group, respectively, as well as any of the predefined outcome measures (primary outcome measure: all-cause mortality at 30 days; secondary outcome measures: in-hospital mortality, in-hospital complications, days on mechanical ventilation, and/or LOS in hospital/ICU).

Risk of bias assessment

The quality of the included studies was assessed by two independent authors (TGE, JSB) using the Cochrane risk of bias assessment tool in Covidence [18], which consists of seven specific domains (random

sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other bias). In each domain the study is judged to have a low, high, or unclear risk of bias.

Summary measures and synthesis of results

This systematic review was expected to be a descriptive summary of the current evidence.

Patient and public involvement

There was no patient involvement in this study.

RESULTS

Our combined search strategy identified 6142 records to be considered for inclusion. After screening titles and abstracts, 60 articles were evaluated in full text for eligibility. An interrater reliability (Cohen's Kappa) of 0.88 (confidence interval (CI): 0.82-0.94) for screening and selecting studies was obtained. After full text review, only one study fulfilled the inclusion criteria and was included in the systematic review [19] (Figure 1). Another study, which did not strictly fulfill the inclusion criteria, was also included for descriptive purposes. Both studies were prospective, interventional trials and included intubated trauma patients, and thus no prospective, interventional trials of spontaneously breathing trauma patients were identified. Characteristics, methods, and results for the two included studies are summarized in Table 1.

Taher et al. [19] performed a randomized study of 68 mechanically ventilated adult patients sustaining severe traumatic brain injury (TBI). The patients were randomized to receive a FiO_2 of either 0.80 (intervention group) or 0.50 (control group) during the first six hours of treatment. A total of 34 patients in each group completed the study. The two groups were similar in terms of age, gender distribution, and GCS on admission. Relevant outcomes for this systematic review were LOS in hospital and LOS in ICU. The study found no statistically significant difference between the intervention and control group in either of these outcomes measures (hospital LOS: 11.4 days (SD: 5.4) vs. 13.9 days (SD: 8.1), respectively, p=0.14; ICU LOS: 9.4 days (SD: 6.6) vs. 11.4 days (SD: 8.4), respectively, p=0.28). No patients in either group died.

The study by Barzilay et al. [20] included 21 adult patients with chest trauma and severe respiratory insufficiency due to flail chest or pulmonary contusion requiring mechanical ventilation. Patients were alternately assigned to two different mechanical ventilation strategies: conventional mechanical ventilation or high-frequency positive pressure with low-rate ventilation. FiO_2 was set to be 0.40 in both groups, but subsequently adjusted to arterial oxygen tension and therefore different between the two groups according to the results. Eleven patients in the intervention group received an estimated mean FiO_2 of 0.45 and had a mean arterial oxygen tension (PaO_2) of 89.91 ± 10.24 mmHg during the first 48 hours after hospital admission. The control group consisted of ten similar patients receiving an estimated mean FiO_2 of 0.60 and had a mean PaO_2 of 78.43 ± 11.13 mmHg during the first 48 hours after hospital admission. Neither of these

FiO_2s were reported in detail, but can be estimated from the data provided in the article. No simple relationship was found between the estimated FiO_2 and PaO_2 values presumably as a consequence of the two different ventilation strategies. Outcomes relevant to this systematic review were days on mechanical ventilation and mortality. The study found no statistically significant difference in days on mechanical ventilation between the intervention group and the control group (4.2 days (SD: 0.91) vs. 6.1 days (SD: 0.8), respectively, $p<0.1$). In terms of mortality, two (20%) patients in the control group died compared to none in the intervention group. The p-value was not reported, but the difference was not statistically significant using Fisher's exact test.

The risk of bias assessment for the included studies is presented in Table 2. In the study by Taher et al., three domains were judged to have a low risk of bias (blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data), none to have a high risk of bias, and four domains to have an unclear risk of bias (random sequence generation, allocation concealment, selective reporting, other bias). The study by Barzilay et al. was judged to have two domains with low risk of bias (blinding of participants and personnel, blinding of outcome assessment), two domains with high risk of bias (allocation concealment, other bias), and three domains with an unclear risk of bias (random sequence generation, incomplete outcome data, selective reporting).

DISCUSSION

Summary of evidence

In this systematic review of interventional trials of the use of supplementary oxygen in the initial treatment of trauma patients, we identified no studies of spontaneously breathing patients, and only one interventional trial of intubated trauma patients was found to fulfill the inclusion criteria. Taher et al. [19] found the low FiO_2 group (0.50) to have slightly longer LOS in hospital and LOS in ICU than the high FiO_2 group (0.80), however, these differences were not statistically significant. Additionally, no patients died in either group. In another study by Barzilay et al. [20], which did not strictly fulfill the inclusion criteria, no statistically significant differences were found between the groups, although patients in the high FiO_2 group (0.60) tended to have a higher mortality and more days on mechanical ventilation than the patients in the low FiO_2 group (0.45). Due to the low number as well as heterogeneity of the included studies, we neither found it possible to pool the results of the two studies, nor to draw any conclusions from these findings.

The rationale for supplementation of oxygen for various patient groups has for decades – and even centuries – seemed self-evident for most health-care providers [21]. Oxygen supplementation, often in excess, has been considered a safe measure rather than an intervention that could potentially be harmful and thus needing a clear indication of administration. Supplementation of oxygen has, until recently, escaped the critical evaluation of its value and indication as is necessary for all other drugs not having the same historical, "self-evident" benefit as is the case for oxygen. As previously described, trauma patient management is mostly based on guideline recommendations including rather liberal and non-specific oxygen supplementation. Thus, it seems surprising that, even though supplementary oxygen is widely used in the treatment of trauma patients and included in international trauma guidelines, this systematic review finds that the evidence for the use of supplementary oxygen for spontaneously breathing trauma patients is non-existing, and for mechanically ventilated trauma patients the evidence is extremely limited and of low quality. In an era of evidence-based medicine these findings seem inappropriate, and we cannot continue to avoid investigating the potential benefits and harms of a drug that is so widely used.

Supplementary oxygen increases the partial pressure of oxygen in the alveoli, thus increasing the oxygen gradient across the alveolar-capillary membrane. This is likely to increase the PaO_2 when oxygenation is impeded by a barrier in the transport of oxygen across the alveolar-capillary membrane. However, that is not common in trauma patients. On the other hand, it can be reasonable to administer supplementary oxygen in order to increase the amount of oxygen in the lungs to prolong the safe apnea time [22].

Both hypoxemia and hyperoxemia may be harmful. Hypoxemia may cause hypoxic neuronal cell death leading to irreversible brain damage, whereas hyperoxemia has been found to increase the risk of pulmonary complications like the formation of atelectases and airway inflammation [23].

The effect of hyperoxia on outcomes following TBI has been investigated in a few retrospective studies. Rincon et al. [24] and Brenner et al. [25] assessed short-term outcomes and they both found hyperoxia to be associated with increased in-hospital mortality compared to normoxia. Additionally, Brenner et al. found that hyperoxia was associated with lower GCS scores at discharge. Another retrospective study by Davis et al. [26] of patients with moderate to severe TBI found both hypoxemia and hyperoxemia to be correlated with decreased survival to discharge compared to patients with normoxia. In contrast, Raj et al. [27] detected no association between hyperoxemia and six-month mortality.

The evidence for the use of supplementary oxygen has been investigated in recently published systematic reviews. In a Cochrane review from 2015 Wetterslev et al. [10] included 28 studies and found no association between perioperative FiO_2 (high: 0.60-0.90 vs. low: 0.30-0.40) and post-operative surgical site infection and mortality. In another Cochrane review of supplementary oxygen for patients with suspected or confirmed acute myocardial infarction (AMI), Cabello et al. [28] included five studies, and they were not able to draw conclusions for or against the use of supplementary oxygen for patients with AMI. Hyperoxia in post-return of spontaneous circulation (ROSC) cardiac arrest (CA) patients has been studied in a systematic review and meta-analysis by Wang et al. [9]. 14 studies were included, and the authors found hyperoxia to be correlated with increased in-hospital mortality in a meta-analysis of eight of the included studies. Finally, Damiani et al. [7] have looked at the association between arterial hyperoxia and mortality for adult ICU patients (mechanically ventilated, post-cardiac arrest, stroke, TBI) in a systematic review and meta-analysis from 2014 of 17 studies. In the meta-analysis hyperoxia was associated with increased mortality for post-

cardiac arrest, stroke, and TBI patients, though the authors report the studies to be rather heterogeneous. As the trauma population is a very heterogeneous and typically a younger and less comorbid group of patients than other critically ill populations (i.e. AMI, CA, stroke) the results of the before-mentioned systematic reviews of other patient populations cannot be extrapolated to the trauma population. However, there seems to be an implication that treatment with excess oxygen and hyperoxia can be harmful or at least not beneficial. This, again, stresses the need for investigating the effects of supplementary oxygen and cases of hyperoxia in the trauma population.

Strengths and limitations

This systematic review was conducted in accordance with the PRISMA-guidelines [14] ensuring a systematic and internationally accepted methodological approach. The strengths of this approach include predefined PICOS criteria used to assess for study eligibility, the use of a wide search string in multiple databases, a structured screening and inclusion process by two independent authors, as well as data collection and risk of bias assessment by the same two independent authors using predetermined forms. Our study is limited by the weaknesses of a systematic review in general: The possibility of missing unpublished studies, which creates a potential publication bias, and the possibility that we did not identify all relevant studies despite our systematic methodology. The patient population we included was defined in rather general terms (i.e. adult trauma patients), which may have increased the heterogeneity of the studies, however, we found this to be necessary in order to increase the clinical relevance of our findings. We wanted to study the initial treatment phase of trauma patients, and chose this to be the first 24 hours after the traumatic incident. This time cut-off was chosen rather arbitrarily and did exclude one potentially eligible study [29]. As per our inclusion criteria for this systematic review, we wanted to include both prehospital and in-hospital studies, however, both included studies investigated in-hospital patients with no data on the prehospital supplementary oxygen treatment. As a large proportion of trauma patients receive prehospital supplementary oxygen [5, 6], it is a limitation not to know whether the per protocol FiO_2-group allocation is the only oxygenation treatment the patient has received since the traumatic incident.

The study by Barzilay et al. was included in the review despite lacking strict adherence to the inclusion criteria. We chose to do this, as evidence in this field proved to be extremely sparse, and we wished to report as much of the existing evidence as possible.

We were only able to include two small studies of mechanically ventilated trauma patients, and two different methods of mechanical ventilation were used in the study by Barzilay et al. Thus, the studies were not suitable for pooling results, and we are neither able to draw any conclusions nor provide recommendations for the FiO_2 for mechanically ventilated trauma patients. Furthermore, as no studies of spontaneously breathing trauma patients were found we cannot provide recommendations for the use of supplementary oxygen for spontaneously breathing trauma patients either.

CONCLUSIONS

In this systematic review of supplementary oxygen for trauma patients in the initial phase of treatment, we identified no interventional trials including spontaneously breathing trauma patients and only two small low quality studies assessing oxygen fraction in intubated trauma patients. Thus, the current practice of liberal oxygen administration must be questioned, and interventional studies of supplementary oxygen should be conducted in trauma patients.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

AUTHOR'S CONTRIBUTIONS

TGE, JSB, JS, and LSR have contributed to conception and design of the study.

TGE and JSB have contributed to the acquisition of data.

TGE, JSB, JS, and LSR have contributed to the analysis and interpretation of data.

TGE, JSB, JS, and LSR have participated in drafting and revising the manuscript critically.

TGE, JSB, JS, and LSR have given their final approval of the manuscript to be submitted.

DATA SHARING STATEMENT

Data sharing is not applicable for this systematic review.

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FIGURES

Figure 1

Figure legends: PRISMA flow diagram of the identification, screening, eligibility, and inclusion process [14]. *One of the included studies [20] did not strictly meet the inclusion criteria, however, it is included for descriptive purposes.

Table 1: Characteristics, methods, and results for the included studies of supplementary oxygen for trauma patients.

	Taher et al. [19]		Bazilay et al. [20]*	
Study characteristics				
Setting	Emergency ward		General ICU	
Period	2014		January 1981 – January 1984	
Geographical location	Hamadan, Iran		Afula, Israel	
Methods				
Aim	*"… to assess the effects of normobaric hyperoxia on clinical neurological outcomes of patients with severe TBIs."*		*"… compare the results using ventilatory method, which combines HFPPV [high-frequency positive-pressure ventilation] and low-rate conventional mechanical ventilation (LRCMV), to the results using conventional mechanical ventilation (CMV) with PEEP."*	
Blinding	Double blinded		Not reported	
Study design	Randomized controlled trial		Interventional, non-randomized	
Inclusion criteria	Age 18-65 years; <6 hours passed since the accident; hemodynamic stability; GCS 3-8		All patients admitted to the ICU with a diagnosis of severe respiratory insufficiency due to flail chest or pulmonary contusion	
Exclusion criteria	Pregnancy; chronic disease such as diabetes mellitus, ischemic heart disease, renal failure, acute pulmonary edema, history of massive myocardial infarction, and heart failure; blood pressure <90/60 mmHg; successful CPR; death or loss to follow-up; patients in the control group in which oxygen therapy was inevitable		Not reported	
	Intervention group	**Control group**	**Intervention group**	**Control group**
Results				
No. of patients	34	34	11	10
Age [years], mean (SD)	39.7 (14.1)	45.7 (13.3)	40.6 (22.45)	39.8 (18.18)
Female sex, no. (%)	9 (26.5)	11 (32.4)	Not reported	Not reported
GCS on admission, mean (SD)	7.4 (0.79)	7.4 (0.89)		
FiO_2, mean (SD)	0.80	0.50	0.45†	0.60†
PaO_2 [mmHg], mean (SD)	Not reported	Not reported	89.91 +/- 10.24†	78.43 +/- 11.13†
Outcome measures				
30 day all-cause mortality, n (%)	0 (0%)	0 (0%)	0 (0%)	2 (20%)
Hospital LOS [days]	11.4 (5.4)	13.9 (8.1)	Not reported	Not reported
ICU LOS [days]	9.4 (6.6)	11.4 (8.4)	Not reported	Not reported
Days on mechanical ventilation, mean (SD)	Not reported	Not reported	4.2 (0.91)	6.1 (0.8)

*This study did not strictly meet the inclusion criteria, however, it was included for descriptive purposes.

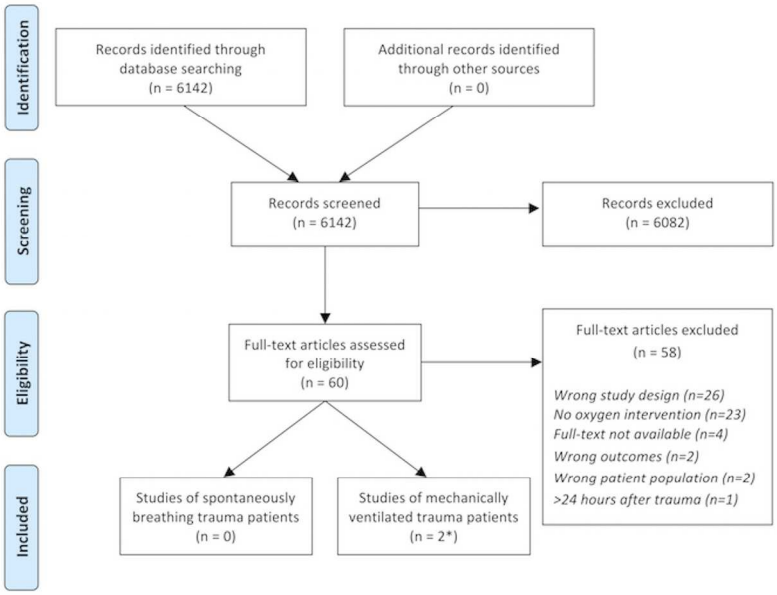
†during first 48 hours in hospital (FiO_2 estimated from other results)

Intensive Care Unit (ICU); Positive end expiratory pressure (PEEP); Traumatic brain injury (TBI); Glasgow Coma Scale Score (GCS); Cardio pulmonary resuscitation (CPR); Standard deviation (SD); inspiratory oxygen fraction (FiO_2); arterial oxygen tension (PaO_2); Length of stay (LOS)

Table 2: Risk of bias assessment for the two included studies.

	Taher et al. [19]		Barzilay et al. [20]*	
Risk of bias domain	**Judgment**	**Support for judgment**	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Unclear	*Quote*: … patients were divided in two groups… ” *Comment*: Not a random component in the sequence generation process.	Unclear	*Comment*: No description of a random component in the sequence generation process.
Allocation concealment (selection bias)	Unclear	*Comment*: No description of allocation concealment.	High	*Quote*: “Patients were assigned alternately to two groups ” *Comment*: Investigators had the possibility of foreseeing the assignment.
Blinding of participants and personnel (performance bias)	Low	Quote: “In this double blind clinical trial… ” Comment: Probably done.	Low	*Comment*: No blinding is described, but the relevant outcomes are not likely to be influences by lack of blinding.
Blinding of outcome assessment (detection bias)	Low	*Comment*: No blinding of outcome assessment is described, but the relevant outcomes are not likely to be influences by lack of blinding.	Low	*Comment*: No blinding of outcome assessment is described, but the relevant outcomes are not likely to be influences by lack of blinding.
Incomplete outcome data (attrition bias)	Low	*Comment*: Outcome is reported for all included patients.	Unclear	*Comment*: The outcomes are not described as being defined before commencing the study.
Selective reporting (reporting bias)	Unclear	*Comment*: No protocol is available and the reported outcomes are not pre-specified in the methods section.	Unclear	*Comment*: As outcomes are not described as being defined before commencing the study, there is insufficient information to assess this domain.
Other bias	Unclear	*Comment*: There is insufficient information on the study design to assess whether an important risk of bias exists.	High	Quote: “Those in the study group were connected to a two-ventilator HFPPV system of our own design” Comment: The authors are likely to have a preference for their own design.

*This study did not strictly meet the inclusion criteria, however, it was included for descriptive purposes.



PRISMA flow diagram of the identification, screening, eligibility, and inclusion process [14]. *One of the included studies [20] did not strictly meet the inclusion criteria, however, it is included for descriptive purposes.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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