

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<u>http://bmjopen.bmj.com</u>).

If you have any questions on BMJ Open's open peer review process please email <u>info.bmjopen@bmj.com</u>

BMJ Open

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2017-020880
Article Type:	Research
Date Submitted by the Author:	01-Dec-2017
Complete List of Authors:	Eskesen, Trine; Rigshospitalet, Department of anesthesia Baekgaard, Josefine; Rigshospitalet, Department of anesthesia Steinmetz, Jacob; Rigshospitalet, Department of anesthesia Rasmussen, Lars; Rigshospitalet, Department of anesthesia
Primary Subject Heading :	Anaesthesia
Secondary Subject Heading:	Emergency medicine
Keywords:	TRAUMA MANAGEMENT, Oxygen, Intubation



2 3		
4 5	1	Initial Use of Supplementary Oxygen For Trauma Patients: A Systematic
6 7	2	Review
8 9 10	3	Trine Grodum Eskesen, BA, trinegeskesen@live.dk ¹
11 12	4	Josefine S. Baekgaard, MD, josefinebaekgaard@me.com ¹
13	5	Jacob Steinmetz, MD, PhD, docsteinmetz@gmail.com ¹
14 15	6	Lars S. Rasmussen, MD, PhD, DMSc, lars.simon.rasmussen.01@regionh.dk ¹
16 17	0	Lars S. Kasinussen, MD, Fild, Divise, lars.sinion.rasinussen.or@regionin.dk
18 19 20	7	¹ Department of Anesthesia, Section 4231, Rigshospitalet, University of Copenhagen, Denmark
20 21 22	8	Corresponding author:
23	9	Trine Grodum Eskesen, BA
24 25	10	E-mail: trinegeskesen@live.dk
26 27	11	Tel.: +45 40 68 83 72
28 29	12	Department of Anesthesia, Section 4231
30 31	13	Tel.: +45 40 68 83 72 Department of Anesthesia, Section 4231 Rigshospitalet Juliane Maries Vej 10 DK-2100 Copenhagen, Denmark
32 33	14	Juliane Maries Vej 10
34 35	15	DK-2100 Copenhagen, Denmark
36 37	16	
38 39	17	
40 41	18	
42 43	19	Keywords: Oxygen; Supplementary oxygen; Intubation; Trauma
44 45	20	
46 47	21	
48 49	22	Word count abstract: 292
50 51	23	Word count manuscript (excluding figure and tables): 2787
52 53	24	
54 55	25	
56 57		
58 59		
60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 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 (FiO₂) for intubated trauma patients in the initial phase of treatment.

Methods: Several databases were systematically searched in September 2017 for studies fulfilling the

6 following criteria: trauma patients (Population); supplementary oxygen/high FiO₂ (Intervention) versus no

7 supplementary oxygen/low FiO₂ (<u>C</u>ontrol) for spontaneously breathing or intubated trauma patients,

8 respectively, in the initial phase of treatment; mortality, complications, days on mechanical ventilation,

9 and/or length of stay (LOS) in hospital/intensive care unit (ICU) (<u>O</u>utcomes); prospective interventional

10 trials (<u>Study design</u>). Two independent reviewers screened and identified studies and extracted data from

11 included studies.

Results: 6142 citations were screened with an inter-rater reliability (Cohen's Kappa) of 0.88. One

13 interventional trial of intubated trauma patients was included. 68 trauma patients were randomized to receive

14 a FiO₂ of 0.80 (intervention group) or 0.50 (control group) during mechanical ventilation (first six hours).

15 There was no significant difference in hospital or ICU LOS between the groups. No patients died in either

16 group. Another interventional trial, not strictly fulfilling the inclusion criteria, was presented for descriptive

17 purposes. 21 trauma patients were alternately assigned to two types of mechanical ventilation (first 48

hours), both aiming at a FiO₂ of 0.40, but resulted in estimated mean FiO₂s 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

Conclusions: Evidence for the use of supplementary oxygen for spontaneously breathing trauma patients is
lacking, and the evidence for low versus high FiO₂ for intubated trauma patients is limited.

Protocol registration: PROSPERO (ID no. 42016050552).

trauma patients were identified.

1 2		
3		
4 5	1	STRENGTHS AND LIMITATIONS
6	2	
7 8	3	Strengths
9 10	4	• The use of predefined PICOS (Population, Intervention, Control, Outcomes, Study design) criteria to
11 12 12	5	assess for study eligibility.
13 14 15	6	• The use of a wide search string in multiple databases.
16 17	7	• The use of a structured screening and inclusion process as well as data collection and risk of bias
18 19	8	assessment by two independent authors.
20	9	
21 22	10	Limitations
23 24 25	11	• There is a possibility of missing unpublished studies, which creates a potential publication bias.
25 26 27	12	• It is possible that we did not identify all relevant studies despite our systematic methodology.
28 29	13	
30 31	14	
32 33	15	
34 35	16	
36 37	17	
38 39 40	18	
40 41 42	19	
43 44	20	
45 46	21	
47 48	22	
49 50	23	
51 52	24	
53 54	25	
55 56		
57 58		
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 3

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright

1	BACKGROUNI
1	BACKGROUNI

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 FiO₂ (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) FiO₂ for

intubated trauma patients.

1 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 MetaAnalyses Protocols (PRISMA-P) [15], and was registered in the International Prospective Register of
Systematic Reviews (PROSPERO) (registration number: CRD42016050552) [16].

8 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) FiO₂ 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.

19 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]

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

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").

13 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

1 2		
3 4	1	sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome
5 6	2	assessment, incomplete outcome data, selective reporting, other bias). In each domain the study is judged to
7 8 9	3	have a low, high, or unclear risk of bias.
9 10 11	4	Summary measures and synthesis of results
12 13	5	This systematic review was expected to be a descriptive summary of the current evidence.
14 15		
15 16 17	6	
18 19	7	
20 21	8	
22 23	9	
24 25	10	
26 27		
28	11	
29 30	12	
31 32	13	
33 34	14	
35 36	15	
37 38	16	
39 40	17	
41	18	
42 43 44	19	
45 46	20	
47 48	21	
49 50	22	
50 51 52	23	
53	24	
54 55	25	
56 57		
58 59		For a construction on the test of the second s
60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

RESULTS

2	Our combined search strategy identified 6142 records to be considered for inclusion. After screening
3	titles and abstracts, 60 articles were evaluated in full text for eligibility. An interrater reliability (Cohen's
4	Kappa) of 0.88 (confidence interval (CI): 0.82-0.94) for screening and selecting studies was obtained. After
5	full text review, only one study fulfilled the inclusion criteria and was included in the systematic review [19]
6	(Figure 1). Another study, which did not strictly fulfill the inclusion criteria, was also included for
7	descriptive purposes. Both studies were prospective, interventional trials and included intubated trauma
8	patients, and thus no prospective, interventional trials of spontaneously breathing trauma patients were
9	identified. Characteristics, methods, and results for the two included studies are summarized in Table 1.
10	Taher et al. [19] performed a randomized study of 68 mechanically ventilated adult patients sustaining
11	severe traumatic brain injury (TBI). The patients were randomized to receive a FiO_2 of either 0.80
12	(intervention group) or 0.50 (control group) during the first six hours of treatment. A total of 34 patients in
13	each group completed the study. The two groups were similar in terms of age, gender distribution, and GCS
14	on admission. Relevant outcomes for this systematic review were LOS in hospital and LOS in ICU. The
15	study found no statistically significant difference between the intervention and control group in either of
16	these outcomes measures (hospital LOS: 11.4 days (SD: 5.4) vs. 13.9 days (SD: 8.1), respectively, p=0.14;
17	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.
18	The study by Barzilay et al. [20] included 21 adult patients with chest trauma and severe respiratory
19	insufficiency due to flail chest or pulmonary contusion requiring mechanical ventilation. Patients were
20	alternately assigned to two different mechanical ventilation strategies: conventional mechanical ventilation
21	or high-frequency positive pressure with low-rate ventilation. FiO_2 was set to be 0.40 in both groups, but
22	subsequently adjusted to arterial oxygen tension and therefore different between the two groups according to
23	the results. Eleven patients in the intervention group received an estimated mean FiO_2 of 0.45 and had a
24	mean arterial oxygen tension (PaO ₂) of 89.91 ± 10.24 mmHg during the first 48 hours after hospital
25	admission. The control group consisted of ten similar patients receiving an estimated mean FiO_2 of 0.60 and
26	had a mean PaO_2 of 78.43 ± 11.13 mmHg during the first 48 hours after hospital admission. Neither of these

1	FiO ₂ s were reported in detail, but can be estimated from table 3 in the article. No simple relationship was
2	found between the estimated FiO ₂ and PaO ₂ values presumably as a consequence of the two different
3	ventilation strategies. Outcomes relevant to this systematic review were days on mechanical ventilation and
4	mortality. The study found no statistically significant difference in days on mechanical ventilation between
5	the intervention group and the control group (4.2 days (SD: 0.91) vs. 6.1 days (SD: 0.8), respectively, p<0.1).
6	In terms of mortality, two (20%) patients in the control group died compared to none in the intervention
7	group. The p-value was not reported, but the difference was not statistically significant using Fisher's exact
8	test.
ç	The risk of bias assessment for the included studies is presented in Table 2. In the study by Taher et al.,
10	three domains were judged to have a low risk of bias (blinding of participants and personnel, blinding of
11	outcome assessment, incomplete outcome data), none to have a high risk of bias, and four domains to have
12	an unclear risk of bias (random sequence generation, allocation concealment, selective reporting, other bias).
13	The study by Barzilay et al. was judged to have two domains with low risk of bias (blinding of participants
14	and personnel, blinding of outcome assessment), two domains with high risk of bias (allocation concealment,
15	other bias), and three domains with an unclear risk of bias (random sequence generation, incomplete
16	outcome data, selective reporting).
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright

1 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 FiO₂ 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.

Page 11 of 23

BMJ Open

1	Supplementary oxygen increases the partial pressure of oxygen in the alveoli, thus increasing the oxygen
2	gradient across the alveolar-capillary membrane. This is likely to increase the PaO ₂ when oxygenation is
3	impeded by a barrier in the transport of oxygen across the alveolar-capillary membrane. However, that is not
4	common in trauma patients. On the other hand, it can be reasonable to administer supplementary oxygen in
5	order to increase the amount of oxygen in the lungs to prolong the safe apnea time [22].
6	The evidence for the use of supplementary oxygen has been investigated in recently published
7	systematic reviews. In a Cochrane review from 2015 Wetterslev et al. [10] included 28 studies and found no
8	association between perioperative FiO ₂ (high: 0.60-0.90 vs. low: 0.30-0.40) and post-operative surgical site
9	infection and mortality. In another Cochrane review of supplementary oxygen for patients with suspected or
10	confirmed acute myocardial infarction (AMI), Cabello et al. [23] included five studies, and they were not
11	able to draw conclusions for or against the use of supplementary oxygen for patients with AMI. Hyperoxia in
12	post-return of spontaneous circulation (ROSC) cardiac arrest (CA) patients has been studied in a systematic
13	review and meta-analysis by Wang et al. [9]. 14 studies were included, and the authors found hyperoxia to be
14	correlated with increased in-hospital mortality in a meta-analysis of eight of the included studies. Finally,
15	Damiani et al. [7] have looked at the association between arterial hyperoxia and mortality for adult ICU
16	patients (mechanically ventilated, post-cardiac arrest, stroke, TBI) in a systematic review and meta-analysis
17	from 2014 of 17 studies. In the meta-analysis hyperoxia was associated with increased mortality for post-
18	cardiac arrest, stroke, and TBI patients, though the authors report the studies to be rather heterogeneous. As
19	the trauma population is a very heterogeneous and typically a younger and less comorbid group of patients
20	than other critically ill populations (i.e. AMI, CA, stroke) the results of the before-mentioned systematic
21	reviews of other patient populations cannot be extrapolated to the trauma population. However, there seems
22	to be an implication that treatment with excess oxygen and hyperoxia can be harmful or at least not
23	beneficial. This, again, stresses the need for investigating the effects of supplementary oxygen and cases of
24	hyperoxia in the trauma population.
25	Strengths and limitations

	1	This systematic review was conducted in accordance with the PRISMA-guidelines [14] ensuring a
	2	systematic and internationally accepted methodological approach. The strengths of this approach include
	3	predefined PICOS criteria used to assess for study eligibility, the use of a wide search string in multiple
1	4	databases, a structured screening and inclusion process by two independent authors, as well as data collection
	5	and risk of bias assessment by the same two independent authors using predetermined forms. Our study is
	6	limited by the weaknesses of a systematic review in general: The possibility of missing unpublished studies,
1	7	which creates a potential publication bias, and the possibility that we did not identify all relevant studies
	8	despite our systematic methodology. The patient population we included was defined in rather general terms
1	9	(i.e. adult trauma patients), which may have increased the heterogeneity of the studies, however, we found
	10	this to be necessary in order to increase the clinical relevance of our findings. We wanted to study the initial
	11	treatment phase of trauma patients, and chose this to be the first 24 hours after the traumatic incident. This
	12	time cut-off was chosen rather arbitrarily and did exclude one potentially eligible study [24]. As per our
	13	inclusion criteria for this systematic review, we wanted to include both prehospital and in-hospital studies,
	14	however, both included studies investigated in-hospital patients with no data on the prehospital
	15	supplementary oxygen treatment. As a large proportion of trauma patients receive prehospital supplementary
	16	oxygen [5, 6], it is a limitation not to know whether the per protocol FiO ₂ -group allocation is the only
1	17	oxygenation treatment the patient has received since the traumatic incident.
	18	The study by Barzilay et al. was included in the review despite lacking strict adherence to the inclusion
	19	criteria. We chose to do this, as evidence in this field proved to be extremely sparse, and we wished to report
	20	as much of the existing evidence as possible.
	21	We were only able to include two small studies of mechanically ventilated trauma patients, and two
	22	different methods of mechanical ventilation were used in the study by Barzilay et al. Thus, the studies were
	23	not suitable for pooling results, and we are neither able to draw any conclusions nor provide
	24	recommendations for the FiO ₂ for mechanically ventilated trauma patients. Furthermore, as no studies of
	25	spontaneously breathing trauma patients were found we cannot provide recommendations for the use of
	26	supplementary oxygen for spontaneously breathing trauma patients either.
	27	

1 2		
3 4	1	CONCLUSIONS
5 6 7	2	In this systematic review of supplementary oxygen for trauma patients in the initial phase of treatment,
7 8	3	we identified no interventional trials including spontaneously breathing trauma patients and only two small
9 10	4	low quality studies assessing oxygen fraction in intubated trauma patients. Thus, the current practice of
11 12	5	liberal oxygen administration must be questioned, and interventional studies of supplementary oxygen
13 14	6	should be conducted in trauma patients.
15 16	7	
17 18	8	
19 20	9	
21 22	10	should be conducted in trauma patients.
23 24	11	
25 26		
27 28	12	
29 30	13	
31 32	14	
33 34	15	
35 36	16	
37 38	17	
39 40	18	
40 41 42	19	
42 43 44	20	
45		
46 47	21	
48 49	22	
50 51	23	
52 53	24	
54 55	25	
56 57		
58 59		For poor review only, http://bmienen.hmi.com/cite/about/guidelines.yhtml 13
60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

1 FUNDING

- 2 Our research group is supported by the Tryg Foundation, however, this research received no specific grant
- 3 from any funding agency in the public, commercial or not-for-profit sectors.

5 COMPETING INTERESTS STATEMENT

6 The authors declare that they have no competing interests.

8 AUTHOR'S CONTRIBUTIONS

- 9 TGE, JSB, JS, and LSR have contributed to conception and design of the study.
- 10 TGE and JSB have contributed to the acquisition of data.
- 11 TGE, JSB, JS, and LSR have contributed to the analysis and interpretation of data.
- 12 TGE, JSB, JS, and LSR have participated in drafting and revising the manuscript critically.
- 13 TGE, JSB, JS, and LSR have given their final approval of the manuscript to be submitted.

- 15 DATA SHARING STATEMENT
- 16 Data sharing is not applicable for this systematic review.

 17

 18

 19

 20

 21

 22

 23

1 2			
3 4	1	REF	ERENCES
5 6 7	2	1.	Surgeons ACo. ATLS Student Course Manual: Advanced Trauma Life Support. 9th edn; 2012.
7 8 9	3	2.	Mortality GBD CoDC. Global, regional, and national age-sex specific all-cause and cause-specific
10 11	4		mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of
12 13	5		Disease Study 2013. Lancet 2015, 385:117-171.
14 15	6	3.	PHTLS. Basic and Advanced Prehospital Trauma Life Support. Revised Fifth edn: Mosby; 2003.
16 17	7	4.	Hale KE, Gavin C, O'Driscoll BR. Audit of oxygen use in emergency ambulances and in a hospital
18 19	8		emergency department. Emerg Med J 2008, 25:773-776.
20 21	9	5.	McMullan J, Rodriquez D, Hart KW, Lindsell CJ, Vonderschmidt K, Wayne B, Branson R. Prevalence
22 23	10		of prehospital hypoxemia and oxygen use in trauma patients. Mil Med 2013, 178:1121-1125.
24 25 26	11	6.	Stockinger ZT, McSwain NE, Jr. Prehospital supplemental oxygen in trauma patients: its efficacy and
26 27 28	12		implications for military medical care. Mil Med 2004, 169:609-612.
29 30	13	7.	Damiani E, Adrario E, Girardis M, Romano R, Pelaia P, Singer M, Donati A. Arterial hyperoxia and
31 32	14		mortality in critically ill patients: a systematic review and meta-analysis. Crit Care 2014, 18:711.
33 34	15	8.	Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, de Jonge E. Association Between Arterial
35 36	16		Hyperoxia and Outcome in Subsets of Critical Illness: A Systematic Review, Meta-Analysis, and
37 38	17		Meta-Regression of Cohort Studies. Crit Care Med 2015, 43:1508-1519.
39 40	18	9.	Wang CH, Chang WT, Huang CH, Tsai MS, Yu PH, Wang AY, Chen NC, Chen WJ. The effect of
41 42	19		hyperoxia on survival following adult cardiac arrest: a systematic review and meta-analysis of
43 44	20		observational studies. Resuscitation 2014, 85:1142-1148.
45 46 47	21	10.	Wetterslev J, Meyhoff CS, Jorgensen LN, Gluud C, Lindschou J, Rasmussen LS. The effects of high
47 48 49	22		perioperative inspiratory oxygen fraction for adult surgical patients. Cochrane Database Syst Rev
50 51	23		2015, 25:CD008884.
52 53			
54 55			
56 57			
58 59			For poor vertice, other (thereice on hereice on (site (shout (avidalines where) 15
60			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

2			
3 4 5	1	11.	Belda FJ, Aguilera L, Garcia de la Asuncion J, Alberti J, Vicente R, Ferrandiz L, Rodriguez R, Company
5 6 7	2		R, Sessler DI, Aguilar G, et al. Supplemental perioperative oxygen and the risk of surgical wound
, 8 9	3		infection: a randomized controlled trial. Jama 2005, 294:2035-2042.
9 10 11	4	12.	Greif R, Akca O, Horn EP, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the
12 13	5		incidence of surgical-wound infection. N Engl J Med 2000, 342:161-167.
14 15	6	13.	Higgins JPT GSe. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0
16 17	7		[updated March 2011]. The Cochrane Collaboration, 2011. Available from
18 19	8		www.handbook.cochrane.org.
20 21	9	14.	Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and
22 23	10		meta-analyses: the PRISMA statement. BMJ 2009, 339:b2535.
24 25	11	15.	Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred
26 27	12		reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst
28 29	13		Rev 2015, 4:1.
30 31	14	16.	PROSPERO, International prospective register of systematic reviews
32 33	15		[https://www.crd.york.ac.uk/PROSPERO/]
34 35	16	17.	Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available
36 37	17		at www.covidence.org
38 39	18	18.	Higgins JPT AD, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins
40 41	19	201	JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0
42 43	20		(updated March 2011). The Cochrane Collaboration, 2011. Available from
44 45 46	20		www.handbook.cochrane.org.
46 47 48	21	19.	Taher A, Pilehvari Z, Poorolajal J, Aghajanloo M. Effects of Normobaric Hyperoxia in Traumatic Brain
40 49 50		19.	
50 51 52	23		Injury: A Randomized Controlled Clinical Trial. Trauma Mon 2016, 21:e26772.
52 53 54			
55 56			
57 58			
50 59 60			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 16

2			
3	1	20.	Barzilay E, Lev A, Ibrahim M, Lesmes C. Traumatic respiratory insufficiency: comparison of
4 5	T	20.	barznay L, Lev A, Ibrahim W, Lesmes C. Tradmatic respiratory insufficiency. comparison of
6 7	2		conventional mechanical ventilation to high-frequency positive pressure with low-rate ventilation.
8 9	3		Crit Care Med 1987, 15:118-121.
10 11	4	21.	Kelly C. Oxygen therapy: time to move on? Ther Adv Respir Dis 2014, 8:191-199.
12 13	5	22.	Edmark L, Kostova-Aherdan K, Enlund M, Hedenstierna G. Optimal oxygen concentration during
14 15	6		induction of general anesthesia. Anesthesiology 2003, 98:28-33.
16 17 19	7	23.	Cabello JB, Burls A, Emparanza JI, Bayliss SE, Quinn T. Oxygen therapy for acute myocardial
18 19 20	8		infarction. Cochrane Database Syst Rev 2016, 12:Cd007160.
21 22	9	24.	Stall A, Paryavi E, Gupta R, Zadnik M, Hui E, O'Toole RV. Perioperative supplemental oxygen to
23 24	10		reduce surgical site infection after open fixation of high-risk fractures: a randomized controlled
25 26	11		pilot trial. J Trauma Acute Care Surg 2013, 75:657-663.
27 28 29	12		pilot trial. J Trauma Acute Care Surg 2013, 75:657-663.
30 31 32	13		
33 34	14		
35 36	15		
30 37 38	16		
39 40	17		
41 42	18		
43 44 45	19 20		
45 46 47	21		
48 49	22		
50 51	23		
52 53	24		
54 55 56	25		
57 58			
59 60			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 17

1	
2 3	
4 5	1
6 7	2
8	3
9 10	4
11 12	5
13 14 15	6
16 17	7
18 19	8
20 21	9
22 23	10
24 25	11
26 27	12
28 29	13
30 31	14
32 33	15
34 35	16
36 37	17
38	18
39 40	19
41 42	20
43 44	21
45 46	22
47 48	23
49 50	24
51 52	25
52 53 54	26
55 56	27
57	
58 59	
60	

1	FIGURES
2	
3	Figure 1
1	Figure legends: PRISMA flow diagram of the identification, screening, eligibility, and inclusion process
5	[14]. *One of the included studies [20] did not strictly meet the inclusion criteria, however, it is included for
5	descriptive purposes.
7	
3	
Э	
)	
1	
2	
3	
1	
5	
5	
7	
_	

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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

2 patients.

	Taher et a	al. [19]	Bazilay et a	I. [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 hyperoxia on clinical n outcomes of patients wi	eurological	" compare the results u method, which combines frequency positive-pressu low-rate conventional me	<i>HFPPV</i> [high- are ventilation] and	
			ventilation (LRCMV), to conventional mechanical with PEEP."	the results using	
Blinding	Double blinded		Not reported		
Study design	Randomized controlled		Interventional, non-rando		
Inclusion criteria	Age 18-65 years; <6 hc the accident; hemodyna 3-8		All patients admitted to the diagnosis of severe respiration due to flail chest or pulm	atory insufficiency	
Exclusion criteria	Pregnancy; chronic dise diabetes mellitus, ische renal failure, acute pulr history of massive myo and heart failure; blood mmHg; successful CPF follow-up; patients in th which oxygen therapy	mic heart disease, nonary edema, cardial infarction, pressure <90/60 c; death or loss to he control group in was inevitable	Not reported		
	Intervention group	Control group	Intervention group	Control group	
Results					
No. of patients	34	34	11	20.0 (10.1	
Age [years], mean (SD)	39.7 (14.1)	45.7 (13.3)	40.6 (22.45)	39.8 (18.1	
Female sex, no. (%)	9 (26.5)	11 (32.4)	Not reported	Not reporte	
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 +/- 10.247	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 report	
ICU LOS [days]	9.4 (6.6)	11.4 (8.4)	Not reported	Not report	
Days on mechanical ventilation, mean (SD)	Not reported	Not reported	4.2 (0.91)	6.1 (0.	

*†*during first 48 hours in hospital (FiO₂ estimated from other results)

5 Intensive Care Unit (ICU); Positive end expiratory pressure (PEEP); Traumatic brain injury (TBI); Glasgow Coma

6 Scale Score (GCS); Cardio pulmonary resuscitation (CPR); Standard deviation (SD); inspiratory oxygen fraction

7 (FiO₂); arterial oxygen tension (PaO₂); Length of stay (LOS)

:

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

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

		Taher et al. [19]	В	arzilay 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	<i>Comment</i> : No description of a random component in the sequence generation process.
Allocation concealment (selection bias)	Unclear	<i>Comment</i> : No description of allocation concealment.	High	Quote: "Patients were assigned alternately to two groups" Comment: Investigators ha the possibility of foreseein the assignment.
Blinding of participants and personnel (performance bias)	Low	Quote: "In this double blind clinical trial" Comment: Probably done.	Low	<i>Comment</i> : 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	<i>Comment</i> : No blinding of outcome assessment is described, but the relevant outcomes are not likely to be influences by lack of blinding.	Low	<i>Comment</i> : No blinding of outcome assessment is described, but the relevan outcomes are not likely to be influences by lack of blinding.
Incomplete outcome data (attrition bias)	Low	<i>Comment</i> : Outcome is reported for all included patients.	Unclear	Comment: The outcomes are not described as being defined before commencin the study.
Selective reporting (reporting bias)	Unclear	<i>Comment</i> : No protocol is available and the reported outcomes are not pre- specified in the methods section.	Unclear	<i>Comment</i> : As outcomes ar not described as being defined before commencir the study, there is insufficient information to assess this domain.
Other bias	Unclear	<i>Comment</i> : 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.

1	
2	
3	
4	
5	
6	
7	
8	
9	Unable to Convert Image
10	
11	The dimensions of this image (in pixels) are too large
12	to be converted. For this image to convert,
13	the total number of pixels (height x width) must be
14	less than 40,000,000 (40 megapixels).
15	less than 40,000,000 (40 megapixels).
16	
17	
18	
19	PRISMA flow diagram of the identification, screening, eligibility, and inclusion process [14]. *One of the
20	included studies [20] did not strictly meet the inclusion criteria, however, it is included for descriptive
21	purposes.
22	
23	
24	
25	
26	
27	
28	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.
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
55	
55	
56	
50 57	
57	
58 59	
60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
00	



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page a
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

Page 22 of 23

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

Page 23 of 23



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	1		
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

41 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. 42 doi:10.1371/journal.pmed1000097 For more information, visit: www.prisma-statement.org.

Page 2 of 2 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

BMJ Open

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2017-020880.R1
Article Type:	Research
Date Submitted by the Author:	30-Jan-2018
Complete List of Authors:	Eskesen, Trine; Rigshospitalet, Department of anesthesia Baekgaard, Josefine; Rigshospitalet, Department of anesthesia Steinmetz, Jacob; Rigshospitalet, Department of anesthesia Rasmussen, Lars; Rigshospitalet, Department of anesthesia
Primary Subject Heading :	Anaesthesia
Secondary Subject Heading:	Emergency medicine
Keywords:	TRAUMA MANAGEMENT, Oxygen, Intubation



2 3		
4 5	1	Initial Use of Supplementary Oxygen For Trauma Patients: A Systematic
6 7	2	Review
8 9 10	3	Trine Grodum Eskesen, BA, trinegeskesen@live.dk ¹
11 12	4	Josefine S. Baekgaard, MD, josefinebaekgaard@me.com ¹
13	5	Jacob Steinmetz, MD, PhD, docsteinmetz@gmail.com ¹
14 15	6	Lars S. Rasmussen, MD, PhD, DMSc, lars.simon.rasmussen.01@regionh.dk ¹
16 17	0	Lars S. Kasinussen, MD, Fild, Divise, lars.sinion.rasinussen.or@regionin.dk
18 19 20	7	¹ Department of Anesthesia, Section 4231, Rigshospitalet, University of Copenhagen, Denmark
20 21 22	8	Corresponding author:
23	9	Trine Grodum Eskesen, BA
24 25	10	E-mail: trinegeskesen@live.dk
26 27	11	Tel.: +45 40 68 83 72
28 29	12	Department of Anesthesia, Section 4231
30 31	13	Tel.: +45 40 68 83 72 Department of Anesthesia, Section 4231 Rigshospitalet Juliane Maries Vej 10 DK-2100 Copenhagen, Denmark
32 33	14	Juliane Maries Vej 10
34 35	15	DK-2100 Copenhagen, Denmark
36 37	16	
38 39	17	
40 41	18	
42 43	19	Keywords: Oxygen; Supplementary oxygen; Intubation; Trauma
44 45	20	
46 47	21	
48 49	22	Word count abstract: 292
50 51	23	Word count manuscript (excluding figure and tables): 2787
52 53	24	
54 55	25	
56 57		
58 59		
60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 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 (FiO₂) for intubated trauma patients in the initial phase of treatment.

Methods: Several databases were systematically searched in September 2017 for studies fulfilling the

6 following criteria: trauma patients (Population); supplementary oxygen/high FiO₂ (Intervention) versus no

7 supplementary oxygen/low FiO₂ (<u>C</u>ontrol) for spontaneously breathing or intubated trauma patients,

8 respectively, in the initial phase of treatment; mortality, complications, days on mechanical ventilation,

9 and/or length of stay (LOS) in hospital/intensive care unit (ICU) (<u>O</u>utcomes); prospective interventional

10 trials (<u>Study design</u>). Two independent reviewers screened and identified studies and extracted data from

11 included studies.

Results: 6142 citations were screened with an inter-rater reliability (Cohen's Kappa) of 0.88. One

13 interventional trial of intubated trauma patients was included. 68 trauma patients were randomized to receive

14 a FiO₂ of 0.80 (intervention group) or 0.50 (control group) during mechanical ventilation (first six hours).

15 There was no significant difference in hospital or ICU LOS between the groups. No patients died in either

16 group. Another interventional trial, not strictly fulfilling the inclusion criteria, was presented for descriptive

17 purposes. 21 trauma patients were alternately assigned to two types of mechanical ventilation (first 48

hours), both aiming at a FiO₂ of 0.40, but resulted in estimated mean FiO₂s 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

Conclusions: Evidence for the use of supplementary oxygen for spontaneously breathing trauma patients is
lacking, and the evidence for low versus high FiO₂ for intubated trauma patients is limited.

Protocol registration: PROSPERO (ID no. 42016050552).

trauma patients were identified.

1 2		
3		
4 5	1	STRENGTHS AND LIMITATIONS
6	2	
7 8	3	Strengths
9 10	4	• The use of predefined PICOS (Population, Intervention, Control, Outcomes, Study design) criteria to
11 12 12	5	assess for study eligibility.
13 14 15	6	• The use of a wide search string in multiple databases.
16 17	7	• The use of a structured screening and inclusion process as well as data collection and risk of bias
18 19	8	assessment by two independent authors.
20	9	
21 22	10	Limitations
23 24 25	11	• There is a possibility of missing unpublished studies, which creates a potential publication bias.
25 26 27	12	• It is possible that we did not identify all relevant studies despite our systematic methodology.
28 29	13	
30 31	14	
32 33	15	
34 35	16	
36 37	17	
38 39 40	18	
40 41 42	19	
43 44	20	
45 46	21	
47 48	22	
49 50	23	
51 52	24	
53 54	25	
55 56		
57 58		
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 3

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright

1 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

23 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) FiO₂ for intubated trauma patients.

BMJ Open

1 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 MetaAnalyses Protocols (PRISMA-P) [15], and was registered in the International Prospective Register of
Systematic Reviews (PROSPERO) (registration number: CRD42016050552) [16].

8 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) FiO₂ 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.

19 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]

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

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").

13 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

1 2		
3 4	1	sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome
5 6	2	assessment, incomplete outcome data, selective reporting, other bias). In each domain the study is judged to
7 8 9	3	have a low, high, or unclear risk of bias.
9 10 11	4	Summary measures and synthesis of results
12 13	5	This systematic review was expected to be a descriptive summary of the current evidence.
14 15		
15 16 17	6	
18 19	7	
20 21	8	
22 23	9	
24 25	10	
26 27		
28	11	
29 30	12	
31 32	13	
33 34	14	
35 36	15	
37 38	16	
39 40	17	
41	18	
42 43 44	19	
45 46	20	
47 48	21	
49 50	22	
50 51 52	23	
53	24	
54 55	25	
56 57		
58 59		For a construction on the test of the second s
60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

RESULTS

2	Our combined search strategy identified 6142 records to be considered for inclusion. After screening
3	titles and abstracts, 60 articles were evaluated in full text for eligibility. An interrater reliability (Cohen's
4	Kappa) of 0.88 (confidence interval (CI): 0.82-0.94) for screening and selecting studies was obtained. After
5	full text review, only one study fulfilled the inclusion criteria and was included in the systematic review [19]
6	(Figure 1). Another study, which did not strictly fulfill the inclusion criteria, was also included for
7	descriptive purposes. Both studies were prospective, interventional trials and included intubated trauma
8	patients, and thus no prospective, interventional trials of spontaneously breathing trauma patients were
9	identified. Characteristics, methods, and results for the two included studies are summarized in Table 1.
10	Taher et al. [19] performed a randomized study of 68 mechanically ventilated adult patients sustaining
11	severe traumatic brain injury (TBI). The patients were randomized to receive a FiO ₂ of either 0.80
12	(intervention group) or 0.50 (control group) during the first six hours of treatment. A total of 34 patients in
13	each group completed the study. The two groups were similar in terms of age, gender distribution, and GCS
14	on admission. Relevant outcomes for this systematic review were LOS in hospital and LOS in ICU. The
15	study found no statistically significant difference between the intervention and control group in either of
16	these outcomes measures (hospital LOS: 11.4 days (SD: 5.4) vs. 13.9 days (SD: 8.1), respectively, p=0.14;
17	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.
18	The study by Barzilay et al. [20] included 21 adult patients with chest trauma and severe respiratory
19	insufficiency due to flail chest or pulmonary contusion requiring mechanical ventilation. Patients were
20	alternately assigned to two different mechanical ventilation strategies: conventional mechanical ventilation
21	or high-frequency positive pressure with low-rate ventilation. FiO_2 was set to be 0.40 in both groups, but
22	subsequently adjusted to arterial oxygen tension and therefore different between the two groups according to
23	the results. Eleven patients in the intervention group received an estimated mean FiO_2 of 0.45 and had a
24	mean arterial oxygen tension (PaO ₂) of 89.91 ± 10.24 mmHg during the first 48 hours after hospital
25	admission. The control group consisted of ten similar patients receiving an estimated mean FiO_2 of 0.60 and
26	had a mean PaO_2 of 78.43 \pm 11.13 mmHg during the first 48 hours after hospital admission. Neither of these

1	FiO ₂ s were reported in detail, but can be estimated from the data provided in the article. No simple
2	relationship was found between the estimated FiO_2 and PaO_2 values presumably as a consequence of the two
3	different ventilation strategies. Outcomes relevant to this systematic review were days on mechanical
4	ventilation and mortality. The study found no statistically significant difference in days on mechanical
5	ventilation between the intervention group and the control group (4.2 days (SD: 0.91) vs. 6.1 days (SD: 0.8),
6	respectively, p<0.1). In terms of mortality, two (20%) patients in the control group died compared to none in
7	the intervention group. The p-value was not reported, but the difference was not statistically significant using
8	Fisher's exact test.
~	

9 The risk of bias assessment for the included studies is presented in Table 2. In the study by Taher et al., 10 three domains were judged to have a low risk of bias (blinding of participants and personnel, blinding of 11 outcome assessment, incomplete outcome data), none to have a high risk of bias, and four domains to have 12 an unclear risk of bias (random sequence generation, allocation concealment, selective reporting, other bias). 13 The study by Barzilay et al. was judged to have two domains with low risk of bias (blinding of participants 14 and personnel, blinding of outcome assessment), two domains with high risk of bias (allocation concealment, 15 other bias), and three domains with an unclear risk of bias (random sequence generation, incomplete

16 outcome data, selective reporting).

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright

1 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 FiO₂ 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.

Page 11 of 23

1	Supplementary oxygen increases the partial pressure of oxygen in the alveoli, thus increasing the oxygen
2	gradient across the alveolar-capillary membrane. This is likely to increase the PaO ₂ when oxygenation is
3	impeded by a barrier in the transport of oxygen across the alveolar-capillary membrane. However, that is not
4	common in trauma patients. On the other hand, it can be reasonable to administer supplementary oxygen in
5	order to increase the amount of oxygen in the lungs to prolong the safe apnea time [22].
6	Both hypoxemia and hyperoxemia may be harmful. Hypoxemia may cause hypoxic neuronal cell death
7	leading to irreversible brain damage, whereas hyperoxemia has been found to increase the risk of pulmonary
8	complications like the formation of atelectases and airway inflammation [23].
9	The evidence for the use of supplementary oxygen has been investigated in recently published
10	systematic reviews. In a Cochrane review from 2015 Wetterslev et al. [10] included 28 studies and found no
11	association between perioperative FiO ₂ (high: 0.60-0.90 vs. low: 0.30-0.40) and post-operative surgical site
12	infection and mortality. In another Cochrane review of supplementary oxygen for patients with suspected or
13	confirmed acute myocardial infarction (AMI), Cabello et al. [24] included five studies, and they were not
14	able to draw conclusions for or against the use of supplementary oxygen for patients with AMI. Hyperoxia in
15	post-return of spontaneous circulation (ROSC) cardiac arrest (CA) patients has been studied in a systematic
16	review and meta-analysis by Wang et al. [9]. 14 studies were included, and the authors found hyperoxia to be
17	correlated with increased in-hospital mortality in a meta-analysis of eight of the included studies. Finally,
18	Damiani et al. [7] have looked at the association between arterial hyperoxia and mortality for adult ICU
19	patients (mechanically ventilated, post-cardiac arrest, stroke, TBI) in a systematic review and meta-analysis
20	from 2014 of 17 studies. In the meta-analysis hyperoxia was associated with increased mortality for post-
21	cardiac arrest, stroke, and TBI patients, though the authors report the studies to be rather heterogeneous. As
22	the trauma population is a very heterogeneous and typically a younger and less comorbid group of patients
23	than other critically ill populations (i.e. AMI, CA, stroke) the results of the before-mentioned systematic
24	reviews of other patient populations cannot be extrapolated to the trauma population. However, there seems
25	to be an implication that treatment with excess oxygen and hyperoxia can be harmful or at least not
26	beneficial. This, again, stresses the need for investigating the effects of supplementary oxygen and cases of
27	hyperoxia in the trauma population.

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright

1 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 FiO₂ 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.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2		
3 4 5	1	CONCLUSIONS
6 7	2	In this systematic review of supplementary oxygen for trauma patients in the initial phase of treatment,
8	3	we identified no interventional trials including spontaneously breathing trauma patients and only two small
9 10	4	low quality studies assessing oxygen fraction in intubated trauma patients. Thus, the current practice of
11 12	5	liberal oxygen administration must be questioned, and interventional studies of supplementary oxygen
13 14	6	should be conducted in trauma patients.
15 16	7	
17 18	8	
19 20	9	
21 22	10	
23 24	11	should be conducted in trauma patients.
25 26	12	
27 28		
29 30	13	
31 32	14	
33 34	15	
35 36	16	
37 38	17	
39 40	18	
41 42	19	
43 44	20	
45 46	21	
47 48		
49 50	22	
51	22	
52 53	23	
54 55	24	
56 57		
58 59		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 13
60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xntml

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

FUNDING

- Our research group is supported by the Tryg Foundation, however, this research received no specific grant
- from any funding agency in the public, commercial or not-for-profit sectors.

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.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2			
3 4	1	REF	ERENCES
5 6 7	2	1.	Surgeons ACo. ATLS Student Course Manual: Advanced Trauma Life Support. 9th edn; 2012.
7 8 9	3	2.	Mortality GBD CoDC. Global, regional, and national age-sex specific all-cause and cause-specific
9 10 11	4		mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of
12 13	5		Disease Study 2013. Lancet 2015, 385:117-171.
14 15	6	3.	PHTLS. Basic and Advanced Prehospital Trauma Life Support. Revised Fifth edn: Mosby; 2003.
16 17	7	4.	Hale KE, Gavin C, O'Driscoll BR. Audit of oxygen use in emergency ambulances and in a hospital
18 19	8		emergency department. Emerg Med J 2008, 25:773-776.
20 21	9	5.	McMullan J, Rodriquez D, Hart KW, Lindsell CJ, Vonderschmidt K, Wayne B, Branson R. Prevalence
22 23	10		of prehospital hypoxemia and oxygen use in trauma patients. Mil Med 2013, 178:1121-1125.
24 25	11	6.	Stockinger ZT, McSwain NE, Jr. Prehospital supplemental oxygen in trauma patients: its efficacy and
26 27 28	12		implications for military medical care. Mil Med 2004, 169:609-612.
28 29 30	13	7.	Damiani E, Adrario E, Girardis M, Romano R, Pelaia P, Singer M, Donati A. Arterial hyperoxia and
31 32	14		mortality in critically ill patients: a systematic review and meta-analysis. Crit Care 2014, 18:711.
33 34	15	8.	Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, de Jonge E. Association Between Arterial
35 36	16		Hyperoxia and Outcome in Subsets of Critical Illness: A Systematic Review, Meta-Analysis, and
37 38	17		Meta-Regression of Cohort Studies. Crit Care Med 2015, 43:1508-1519.
39 40	18	9.	Wang CH, Chang WT, Huang CH, Tsai MS, Yu PH, Wang AY, Chen NC, Chen WJ. The effect of
41 42	19		hyperoxia on survival following adult cardiac arrest: a systematic review and meta-analysis of
43 44	20		observational studies. Resuscitation 2014, 85:1142-1148.
45 46	21	10.	Wetterslev J, Meyhoff CS, Jorgensen LN, Gluud C, Lindschou J, Rasmussen LS. The effects of high
47 48 49	22		perioperative inspiratory oxygen fraction for adult surgical patients. Cochrane Database Syst Rev
50 51	23		2015, 25:CD008884.
52 53			
54 55			
56 57			
58 59			For recorded when the latter (there is non-basic core (site (shout (suidalines when) 15
60			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

2			
3 4 5	1	11.	Belda FJ, Aguilera L, Garcia de la Asuncion J, Alberti J, Vicente R, Ferrandiz L, Rodriguez R, Company
5 6 7	2		R, Sessler DI, Aguilar G, et al. Supplemental perioperative oxygen and the risk of surgical wound
, 8 9	3		infection: a randomized controlled trial. Jama 2005, 294:2035-2042.
9 10 11	4	12.	Greif R, Akca O, Horn EP, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the
12 13	5		incidence of surgical-wound infection. N Engl J Med 2000, 342:161-167.
14 15	6	13.	Higgins JPT GSe. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0
16 17	7		[updated March 2011]. The Cochrane Collaboration, 2011. Available from
18 19	8		www.handbook.cochrane.org.
20 21	9	14.	Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and
22 23	10		meta-analyses: the PRISMA statement. BMJ 2009, 339:b2535.
24 25	11	15.	Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred
26 27	12		reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst
28 29	13		Rev 2015, 4:1.
30 31	14	16.	PROSPERO, International prospective register of systematic reviews
32 33	15		[https://www.crd.york.ac.uk/PROSPERO/]
34 35	16	17.	Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available
36 37	17		at www.covidence.org
38 39	18	18.	Higgins JPT AD, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins
40 41	19	201	JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0
42 43	20		(updated March 2011). The Cochrane Collaboration, 2011. Available from
44 45 46	20		www.handbook.cochrane.org.
46 47 48	21	19.	Taher A, Pilehvari Z, Poorolajal J, Aghajanloo M. Effects of Normobaric Hyperoxia in Traumatic Brain
40 49 50		19.	
50 51 52	23		Injury: A Randomized Controlled Clinical Trial. Trauma Mon 2016, 21:e26772.
52 53 54			
55 56			
57 58			
50 59 60			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 16

2			
3 4	1	20.	Barzilay E, Lev A, Ibrahim M, Lesmes C. Traumatic respiratory insufficiency: comparison of
5			
6 7	2		conventional mechanical ventilation to high-frequency positive pressure with low-rate ventilation.
, 8 9	3		Crit Care Med 1987, 15:118-121.
10 11	4	21.	Kelly C. Oxygen therapy: time to move on? Ther Adv Respir Dis 2014, 8:191-199.
12 13	5	22.	Edmark L, Kostova-Aherdan K, Enlund M, Hedenstierna G. Optimal oxygen concentration during
14 15	6		induction of general anesthesia. Anesthesiology 2003, 98:28-33.
16 17 18	7	23.	Helmerhorst HJ, Schultz MJ, van der Voort PH, de Jonge E, van Westerloo DJ. Bench-to-bedside
18 19 20	8		review: the effects of hyperoxia during critical illness. Crit Care 2015, 19:284.
20 21 22	9	24.	Cabello JB, Burls A, Emparanza JI, Bayliss SE, Quinn T. Oxygen therapy for acute myocardial
23	10		infarction. Cochrane Database Syst Rev 2016, 12:Cd007160.
24 25 26	11	25.	Stall A, Paryavi E, Gupta R, Zadnik M, Hui E, O'Toole RV. Perioperative supplemental oxygen to
27 28	12		reduce surgical site infection after open fixation of high-risk fractures: a randomized controlled
29 30	13		pilot trial. J Trauma Acute Care Surg 2013, 75:657-663.
31 32 33	14		
34 35 36	15		
37 38	16		
39 40 41	17		
42	18		
43 44	19		
45 46	20		
47 48	21		
49 50	22		
51 52	23		
53 54	24		
55 56	25		
57 58			
59 60			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 17

1	
2 3	
4 5	1
6 7	2
8	3
9 10	4
11 12	5
13 14 15	6
16 17	7
18 19	8
20 21	9
22 23	10
24 25	11
26 27	12
28 29	13
30 31	14
32 33	15
34 35	16
36 37	17
38	18
39 40	19
41 42	20
43 44	21
45 46	22
47 48	23
49 50	24
51 52	25
52 53 54	26
55 56	27
57	
58 59	
60	

1	FIGURES
2	
3	Figure 1
1	Figure legends: PRISMA flow diagram of the identification, screening, eligibility, and inclusion process
5	[14]. *One of the included studies [20] did not strictly meet the inclusion criteria, however, it is included for
5	descriptive purposes.
7	
3	
Э	
)	
1	
2	
3	
1	
5	
5	
7	
_	

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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

2 patients.

	Taher et a	ıl. [19]	Bazilay et a	I. [20]*
Study characteristics				
Setting	Emergency ward		General ICU	
Period	2014		January 1981 – January 1	984
Geographical location	Hamadan, Iran		Afula, Israel	
Methods				
Aim	" to assess the effects hyperoxia on clinical n outcomes of patients wi	eurological	" compare the results u method, which combines frequency positive-pressu low-rate conventional me ventilation (LRCMV), to conventional mechanical with PEEP."	HFPPV [high- tre ventilation] and cchanical the results using
Blinding	Double blinded		Not reported	
Study design	Randomized controlled	trial	Interventional, non-rando	
Inclusion criteria	Age 18-65 years; <6 hc the accident; hemodyna 3-8	ours passed since	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	1
Age [years], mean (SD)	39.7 (14.1)	45.7 (13.3)	40.6 (22.45)	<u>39.8 (18.18</u>
Female sex, no. (%)	9 (26.5)	11 (32.4)	Not reported	Not reporte
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 reporte
ICU LOS [days]	9.4 (6.6)	11.4 (8.4)	Not reported	Not reporte
Days on mechanical ventilation,	Not reported	Not reported	4.2 (0.91)	6.1 (0.8

 \ddagger during first 48 hours in hospital (FiO₂ estimated from other results)

5 Intensive Care Unit (ICU); Positive end expiratory pressure (PEEP); Traumatic brain injury (TBI); Glasgow Coma

6 Scale Score (GCS); Cardio pulmonary resuscitation (CPR); Standard deviation (SD); inspiratory oxygen fraction

7 (FiO₂); arterial oxygen tension (PaO₂); Length of stay (LOS)

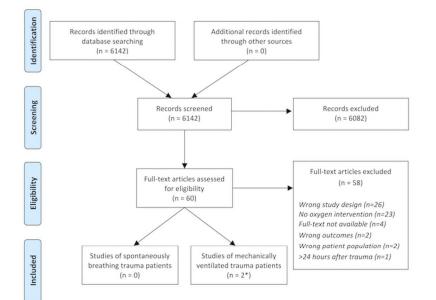
C.

1 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	<i>Comment</i> : No description of a random component in the sequence generation process.	
Allocation concealment (selection bias)	Unclear	<i>Comment</i> : No description of allocation concealment.	High	Quote: "Patients were assigned alternately to two groups" Comment: Investigators ha the possibility of foreseein the assignment.	
Blinding of participants and personnel (performance bias)	Low	Quote: "In this double blind clinical trial" Comment: Probably done.	Low	<i>Comment</i> : 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	<i>Comment</i> : No blinding of outcome assessment is described, but the relevant outcomes are not likely to be influences by lack of blinding.	Low	<i>Comment</i> : No blinding of outcome assessment is described, but the relevan outcomes are not likely to be influences by lack of blinding.	
Incomplete outcome data (attrition bias)	Low	<i>Comment</i> : Outcome is reported for all included patients.	Unclear	Comment: The outcomes are not described as being defined before commencin the study.	
Selective reporting (reporting bias)	Unclear	<i>Comment</i> : No protocol is available and the reported outcomes are not pre- specified in the methods section.	Unclear	<i>Comment</i> : As outcomes ar not described as being defined before commencir the study, there is insufficient information to assess this domain.	
Other bias	Unclear	<i>Comment</i> : 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 a
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

Page 22 of 23

Page 23 of 23



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	1		
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

41 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. 42 doi:10.1371/journal.pmed1000097 For more information, visit: www.prisma-statement.org.

Page 2 of 2 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2017-020880.R2
Article Type:	Research
Date Submitted by the Author:	20-Apr-2018
Complete List of Authors:	Eskesen, Trine; Rigshospitalet, Department of anesthesia Baekgaard, Josefine; Rigshospitalet, Department of anesthesia Steinmetz, Jacob; Rigshospitalet, Department of anesthesia Rasmussen, Lars; Rigshospitalet, Department of anesthesia
Primary Subject Heading :	Anaesthesia
Secondary Subject Heading:	Emergency medicine
Keywords:	TRAUMA MANAGEMENT, Oxygen, Intubation



2 3		
3 4 5	1	Initial Use of Supplementary Oxygen For Trauma Patients: A Systematic
6 7	2	Review
8 9 10	3	Trine Grodum Eskesen, BA, trinegeskesen@live.dk ¹
11 12	4	Josefine S. Baekgaard, MD, josefinebaekgaard@me.com ¹
13 14	5	Jacob Steinmetz, MD, PhD, docsteinmetz@gmail.com ¹
15 16	6	Lars S. Rasmussen, MD, PhD, DMSc, lars.simon.rasmussen.01@regionh.dk ¹
17		
18 19 20	7	¹ Department of Anesthesia, Section 4231, Rigshospitalet, University of Copenhagen, Denmark
20 21	8	Corresponding author:
22 23	9	Trine Grodum Eskesen, BA
24 25	10	E-mail: trinegeskesen@live.dk
26 27	11	Tel.: +45 40 68 83 72
28 29	12	Department of Anesthesia, Section 4231
30 31	13	Rigshospitalet
32 33	14	Juliane Maries Vej 10
34 35	15	Tel.: +45 40 68 83 72 Department of Anesthesia, Section 4231 Rigshospitalet Juliane Maries Vej 10 DK-2100 Copenhagen, Denmark
36 37	16	
38 39	17	
40 41	18	
42 43	19	Keywords: Oxygen; Supplementary oxygen; Intubation; Trauma
44 45	20	
46 47	21	
48 49	22	Word count abstract: 292
50 51	23	Word count manuscript (excluding figure and tables): 2968
52 53	24	
55 54 55	25	
56	_	
57 58		
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 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 (FiO₂) for intubated trauma patients in the initial phase of treatment.

Methods: Several databases were systematically searched in September 2017 for studies fulfilling the

6 following criteria: trauma patients (Population); supplementary oxygen/high FiO₂ (Intervention) versus no

7 supplementary oxygen/low FiO₂ (<u>C</u>ontrol) for spontaneously breathing or intubated trauma patients,

8 respectively, in the initial phase of treatment; mortality, complications, days on mechanical ventilation,

9 and/or length of stay (LOS) in hospital/intensive care unit (ICU) (<u>O</u>utcomes); prospective interventional

10 trials (<u>Study design</u>). Two independent reviewers screened and identified studies and extracted data from

11 included studies.

Results: 6142 citations were screened with an inter-rater reliability (Cohen's Kappa) of 0.88. One

13 interventional trial of intubated trauma patients was included. 68 trauma patients were randomized to receive

14 a FiO₂ of 0.80 (intervention group) or 0.50 (control group) during mechanical ventilation (first six hours).

15 There was no significant difference in hospital or ICU LOS between the groups. No patients died in either

16 group. Another interventional trial, not strictly fulfilling the inclusion criteria, was presented for descriptive

17 purposes. 21 trauma patients were alternately assigned to two types of mechanical ventilation (first 48

hours), both aiming at a FiO₂ of 0.40, but resulted in estimated mean FiO₂s 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

Conclusions: Evidence for the use of supplementary oxygen for spontaneously breathing trauma patients is
lacking, and the evidence for low versus high FiO₂ for intubated trauma patients is limited.

Protocol registration: PROSPERO (ID no. 42016050552).

trauma patients were identified.

1 2								
3								
4 5	1	STRENGTHS AND LIMITATIONS						
6	2							
7 8 9	3	Strengths						
10	4	• The use of predefined PICOS (Population, Intervention, Control, Outcomes, Study design) criteria to						
11 12 13	5	assess for study eligibility.						
14	6	• The use of a wide search string in multiple databases.						
15 16 17	7	• The use of a structured screening and inclusion process as well as data collection and risk of bias						
18 19	8	assessment by two independent authors.						
20	9							
21 22	10	Limitations						
23 24 25	11	• There is a possibility of missing unpublished studies, which creates a potential publication bias.						
25 26 27	12	• It is possible that we did not identify all relevant studies despite our systematic methodology.						
27 28 29	13							
30 31	14							
32 33	15							
34 35	16							
36 37	17							
38 39	18							
40 41	19							
42 43 44	20							
45 46	21							
47 48	22							
49 50	23							
51 52	24							
53 54	25							
55 56								
57 58								
58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 3						

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright

1 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

23 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) FiO₂ for

25 intubated trauma patients.

BMJ Open

1 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 MetaAnalyses Protocols (PRISMA-P) [15], and was registered in the International Prospective Register of
Systematic Reviews (PROSPERO) (registration number: CRD42016050552) [16].

8 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) FiO₂ 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.

19 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").

13 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

1 2		
3		
4 5	1	sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome
6 7	2	assessment, incomplete outcome data, selective reporting, other bias). In each domain the study is judged to
7 8 9	3	have a low, high, or unclear risk of bias.
10 11	4	Summary measures and synthesis of results
12 13	5	This systematic review was expected to be a descriptive summary of the current evidence.
14 15 16	6	Patient and public involvement
17 18	7	There was no patient involvement in this study.
19		
20 21	8	
22		
23	9	
24 25	10	
26	10	
27	11	
28 29	12	
30	12	
31	13	
32 33	1.4	
33 34	14	
35	15	
36		
37 38	16	
39	17	
40		
41 42	18	
43	19	
44		
45 46	20	
47	21	
48		
49 50	22	
51	23	
52	25	
53 54	24	
55 56	25	
50 57		
58		
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 7
00		

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

2	Our combined search strategy identified 6142 records to be considered for inclusion. After screening
3	titles and abstracts, 60 articles were evaluated in full text for eligibility. An interrater reliability (Cohen's
4	Kappa) of 0.88 (confidence interval (CI): 0.82-0.94) for screening and selecting studies was obtained. After
5	full text review, only one study fulfilled the inclusion criteria and was included in the systematic review [19]
6	(Figure 1). Another study, which did not strictly fulfill the inclusion criteria, was also included for
7	descriptive purposes. Both studies were prospective, interventional trials and included intubated trauma
8	patients, and thus no prospective, interventional trials of spontaneously breathing trauma patients were
9	identified. Characteristics, methods, and results for the two included studies are summarized in Table 1.
10	Taher et al. [19] performed a randomized study of 68 mechanically ventilated adult patients sustaining
11	severe traumatic brain injury (TBI). The patients were randomized to receive a FiO_2 of either 0.80
12	(intervention group) or 0.50 (control group) during the first six hours of treatment. A total of 34 patients in
13	each group completed the study. The two groups were similar in terms of age, gender distribution, and GCS
14	on admission. Relevant outcomes for this systematic review were LOS in hospital and LOS in ICU. The
15	study found no statistically significant difference between the intervention and control group in either of
16	these outcomes measures (hospital LOS: 11.4 days (SD: 5.4) vs. 13.9 days (SD: 8.1), respectively, p=0.14;
17	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.
18	The study by Barzilay et al. [20] included 21 adult patients with chest trauma and severe respiratory
19	insufficiency due to flail chest or pulmonary contusion requiring mechanical ventilation. Patients were
20	alternately assigned to two different mechanical ventilation strategies: conventional mechanical ventilation
21	or high-frequency positive pressure with low-rate ventilation. FiO_2 was set to be 0.40 in both groups, but
22	subsequently adjusted to arterial oxygen tension and therefore different between the two groups according to
23	the results. Eleven patients in the intervention group received an estimated mean FiO_2 of 0.45 and had a
24	mean arterial oxygen tension (PaO ₂) of 89.91 ± 10.24 mmHg during the first 48 hours after hospital
25	admission. The control group consisted of ten similar patients receiving an estimated mean FiO ₂ of 0.60 and
26	had a mean PaO_2 of 78.43 ± 11.13 mmHg during the first 48 hours after hospital admission. Neither of these

FiO₂s were reported in detail, but can be estimated from the data provided in the article. No simple relationship was found between the estimated FiO₂ and PaO₂ 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.

9 The risk of bias assessment for the included studies is presented in Table 2. In the study by Taher et al., 10 three domains were judged to have a low risk of bias (blinding of participants and personnel, blinding of 11 outcome assessment, incomplete outcome data), none to have a high risk of bias, and four domains to have 12 an unclear risk of bias (random sequence generation, allocation concealment, selective reporting, other bias). 13 The study by Barzilay et al. was judged to have two domains with low risk of bias (blinding of participants 14 and personnel, blinding of outcome assessment), two domains with high risk of bias (allocation concealment, 15 other bias), and three domains with an unclear risk of bias (random sequence generation, incomplete

16 outcome data, selective reporting).

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright

1 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 FiO₂ 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.

2							
3 4	1	Supplementary oxygen increases the partial pressure of oxygen in the alveoli, thus increasing the oxygen					
4 5	-	supprementary oxygen mercuses the partial pressure of oxygen in the arveon, thus mercusing the oxyg					
6 7	2	gradient across the alveolar-capillary membrane. This is likely to increase the PaO_2 when oxygenation is					
8	3	impeded by a barrier in the transport of oxygen across the alveolar-capillary membrane. However, that is no					
9 10	4	common in trauma patients. On the other hand, it can be reasonable to administer supplementary oxygen in					
11 12	5	order to increase the amount of oxygen in the lungs to prolong the safe apnea time [22].					
13 14	6	Both hypoxemia and hyperoxemia may be harmful. Hypoxemia may cause hypoxic neuronal cell death					
15 16	7	leading to irreversible brain damage, whereas hyperoxemia has been found to increase the risk of pulmonary					
17 18	8	complications like the formation of atelectases and airway inflammation [23].					
19 20	9	The effect of hyperoxia on outcomes following TBI has been investigated in a few retrospective studies.					
21 22	10	Rincon et al. [24] and Brenner et al. [25] assessed short-term outcomes and they both found hyperoxia to be					
23 24	11	associated with increased in-hospital mortality compared to normoxia. Additionally, Brenner et al. found that					
25 26	12	hyperoxia was associated with lower GCS scores at discharge. Another retrospective study by Davis et al.					
27 28	13	[26] of patients with moderate to severe TBI found both hypoxemia and hyperoxemia to be correlated with					
29 30	14	decreased survival to discharge compared to patients with normoxia. In contrast, Raj et al. [27] detected no					
31 32	15	association between hyperoxemia and six-month mortality.					
33 34	16	The evidence for the use of supplementary oxygen has been investigated in recently published					
35 36	17	systematic reviews. In a Cochrane review from 2015 Wetterslev et al. [10] included 28 studies and found					
37 38	18	association between perioperative FiO ₂ (high: 0.60-0.90 vs. low: 0.30-0.40) and post-operative surgical					
39 40	19	infection and mortality. In another Cochrane review of supplementary oxygen for patients with suspected or					
41 42	20	confirmed acute myocardial infarction (AMI), Cabello et al. [28] included five studies, and they were not					
43 44	21	able to draw conclusions for or against the use of supplementary oxygen for patients with AMI. Hyperoxia in					
45 46	22	post-return of spontaneous circulation (ROSC) cardiac arrest (CA) patients has been studied in a systematic					
47 48	23	review and meta-analysis by Wang et al. [9]. 14 studies were included, and the authors found hyperoxia to be					
49 50	24	correlated with increased in-hospital mortality in a meta-analysis of eight of the included studies. Finally,					
51		Damiani et al. [7] have looked at the association between arterial hyperoxia and mortality for adult ICU					
53 54	26	patients (mechanically ventilated, post-cardiac arrest, stroke, TBI) in a systematic review and meta-analysis					
55 56 57 58	27	from 2014 of 17 studies. In the meta-analysis hyperoxia was associated with increased mortality for post-					

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright

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.

1		
2 3		
4	1	The study by Barzilay et al. was included in the review despite lacking strict adherence to the inclusion
5 6	2	criteria. We chose to do this, as evidence in this field proved to be extremely sparse, and we wished to report
7 8	3	as much of the existing evidence as possible.
9 10	4	We were only able to include two small studies of mechanically ventilated trauma patients, and two
11 12	5	different methods of mechanical ventilation were used in the study by Barzilay et al. Thus, the studies were
13 14	6	not suitable for pooling results, and we are neither able to draw any conclusions nor provide
15 16	7	recommendations for the FiO ₂ for mechanically ventilated trauma patients. Furthermore, as no studies of
17 18	8	spontaneously breathing trauma patients were found we cannot provide recommendations for the use of
19 20	9	spontaneously breathing trauma patients were found we cannot provide recommendations for the use of supplementary oxygen for spontaneously breathing trauma patients either.
21 22	10	
23		
24 25	11	
25 26 27	12	
27 28 29	13	
30 31	14	
32	4 5	
33	15	
34 35	16	
36		
37	17	
38	10	
39 40	18	
41	19	
42		
43 44	20	
45		
46	21	
47	22	
48 49	22	
	23	
51		
52	24	
53 54		
54 55	25	
56		
57		
58		
59		1

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.

7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2		
3 4	1	FUNDING
5 6	2	Our research group is supported by the Tryg Foundation, however, this research received no specific grant
7 8	3	from any funding agency in the public, commercial or not-for-profit sectors.
9 10		
11 12	4	
13 14	5	COMPETING INTERESTS STATEMENT
15 16	6	The authors declare that they have no competing interests.
17 18		
19 20	7	
21 22		
23	8	AUTHOR'S CONTRIBUTIONS
24 25	9	TGE, JSB, JS, and LSR have contributed to conception and design of the study.
26 27	10	TGE and JSB have contributed to the acquisition of data.
28 29	11	TGE, JSB, JS, and LSR have contributed to the analysis and interpretation of data.
30 31	12	TGE, JSB, JS, and LSR have participated in drafting and revising the manuscript critically.
32 33	13	TGE, JSB, JS, and LSR have given their final approval of the manuscript to be submitted.
34 35	14	
36	15	DATA SHARING STATEMENT
37 38 39	16	
40 41	17	Data sharing is not applicable for this systematic review.
42 43	18	
44 45	19	
46		
47 48	20	
49 50	21	
51 52	22	
53 54	23	
55 56		
57		
58 59		For poor review only, http://bmionon.hmi.com/cita/about/avidalines.yhtml 15
60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1

2			
3 4	1	REF	ERENCES
5 6 7	2	1.	Surgeons ACo. ATLS Student Course Manual: Advanced Trauma Life Support. 9th edn; 2012.
8 9	3	2.	Mortality GBD CoDC. Global, regional, and national age-sex specific all-cause and cause-specific
10 11	4		mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of
12 13	5		Disease Study 2013. Lancet 2015, 385:117-171.
14 15	6	3.	PHTLS. Basic and Advanced Prehospital Trauma Life Support. Revised Fifth edn: Mosby; 2003.
16 17	7	4.	Hale KE, Gavin C, O'Driscoll BR. Audit of oxygen use in emergency ambulances and in a hospital
18 19	8		emergency department. Emerg Med J 2008, 25:773-776.
20 21	9	5.	McMullan J, Rodriquez D, Hart KW, Lindsell CJ, Vonderschmidt K, Wayne B, Branson R. Prevalence
22 23	10		of prehospital hypoxemia and oxygen use in trauma patients. Mil Med 2013, 178:1121-1125.
24 25	11	6.	Stockinger ZT, McSwain NE, Jr. Prehospital supplemental oxygen in trauma patients: its efficacy and
26 27 28	12		implications for military medical care. Mil Med 2004, 169:609-612.
28 29 30	13	7.	Damiani E, Adrario E, Girardis M, Romano R, Pelaia P, Singer M, Donati A. Arterial hyperoxia and
31 32	14		mortality in critically ill patients: a systematic review and meta-analysis. Crit Care 2014, 18:711.
33 34	15	8.	Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, de Jonge E. Association Between Arterial
35 36	16		Hyperoxia and Outcome in Subsets of Critical Illness: A Systematic Review, Meta-Analysis, and
37 38	17		Meta-Regression of Cohort Studies. Crit Care Med 2015, 43:1508-1519.
39 40	18	9.	Wang CH, Chang WT, Huang CH, Tsai MS, Yu PH, Wang AY, Chen NC, Chen WJ. The effect of
41 42	19		hyperoxia on survival following adult cardiac arrest: a systematic review and meta-analysis of
43 44	20		observational studies. Resuscitation 2014, 85:1142-1148.
45 46	21	10.	Wetterslev J, Meyhoff CS, Jorgensen LN, Gluud C, Lindschou J, Rasmussen LS. The effects of high
47 48 49	22		perioperative inspiratory oxygen fraction for adult surgical patients. Cochrane Database Syst Rev
50 51	23		2015, 25:CD008884.
52 53			
54 55			
56 57			
58 59			1 6
60			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 17 of 24

1 2			
3 4	1	11.	Belda FJ, Aguilera L, Garcia de la Asuncion J, Alberti J, Vicente R, Ferrandiz L, Rodriguez R, Company
5 6 7	2		R, Sessler DI, Aguilar G, et al. Supplemental perioperative oxygen and the risk of surgical wound
7 8 9	3		infection: a randomized controlled trial. Jama 2005, 294:2035-2042.
10 11	4	12.	Greif R, Akca O, Horn EP, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the
12 13	5		incidence of surgical-wound infection. N Engl J Med 2000, 342:161-167.
14 15	6	13.	Higgins JPT GSe. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0
16 17	7		[updated March 2011]. The Cochrane Collaboration, 2011. Available from
18 19	8		www.handbook.cochrane.org.
20 21	9	14.	Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and
22 23	10		meta-analyses: the PRISMA statement. BMJ 2009, 339:b2535.
24 25	11	15.	Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred
26 27	12		reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst
28 29	13		Rev 2015, 4:1.
30 31 32	14	16.	PROSPERO, International prospective register of systematic reviews
33 34	15		[https://www.crd.york.ac.uk/PROSPERO/]
35 36	16	17.	Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available
37 38	17		at <u>www.covidence.org</u>
39 40	18	18.	Higgins JPT AD, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins
41 42	19		JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0
43 44	20		(updated March 2011). The Cochrane Collaboration, 2011. Available from
45 46	21		www.handbook.cochrane.org.
47 48	22	19.	Taher A, Pilehvari Z, Poorolajal J, Aghajanloo M. Effects of Normobaric Hyperoxia in Traumatic Brain
49 50	23		Injury: A Randomized Controlled Clinical Trial. Trauma Mon 2016, 21:e26772.
51 52 53			
54 55			
56 57			
58 59			47
60			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 17

BMJ Open: first published as 10.1136/bmjopen-2017-020880 on 6 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

BMJ Open

1

2			
3 4 5	1	20.	Barzilay E, Lev A, Ibrahim M, Lesmes C. Traumatic respiratory insufficiency: comparison of
5 6 7	2		conventional mechanical ventilation to high-frequency positive pressure with low-rate ventilation.
, 8 9	3		Crit Care Med 1987, 15:118-121.
10 11	4	21.	Kelly C. Oxygen therapy: time to move on? Ther Adv Respir Dis 2014, 8:191-199.
12 13	5	22.	Edmark L, Kostova-Aherdan K, Enlund M, Hedenstierna G. Optimal oxygen concentration during
14 15	6		induction of general anesthesia. Anesthesiology 2003, 98:28-33.
16 17	7	23.	Helmerhorst HJ, Schultz MJ, van der Voort PH, de Jonge E, van Westerloo DJ. Bench-to-bedside
18 19	8		review: the effects of hyperoxia during critical illness. Crit Care 2015, 19:284.
20 21	9	24.	Rincon F, Kang J, Vibbert M, Urtecho J, Athar MK, Jallo J. Significance of arterial hyperoxia and
22 23 24	10		relationship with case fatality in traumatic brain injury: a multicentre cohort study. J Neurol
24 25 26	11		Neurosurg Psychiatry 2014, 85:799-805.
27 28	12	25.	Brenner M, Stein D, Hu P, Kufera J, Wooford M, Scalea T. Association between early hyperoxia and
29 30	13		worse outcomes after traumatic brain injury. Arch Surg 2012, 147:1042-1046.
31 32	14	26.	Davis DP, Meade W, Sise MJ, Kennedy F, Simon F, Tominaga G, Steele J, Coimbra R. Both hypoxemia
33 34	15		and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury. J
35 36	16		Neurotrauma 2009, 26:2217-2223.
37 38	17	27.	Raj R, Bendel S, Reinikainen M, Kivisaari R, Siironen J, Lang M, Skrifvars M. Hyperoxemia and long-
39 40	18		term outcome after traumatic brain injury. Crit Care 2013, 17:R177.
41 42 43	19	28.	Cabello JB, Burls A, Emparanza JI, Bayliss SE, Quinn T. Oxygen therapy for acute myocardial
43 44 45	20		infarction. Cochrane Database Syst Rev 2016, 12:Cd007160.
46 47	21	29.	Stall A, Paryavi E, Gupta R, Zadnik M, Hui E, O'Toole RV. Perioperative supplemental oxygen to
48 49	22		reduce surgical site infection after open fixation of high-risk fractures: a randomized controlled
50 51	23		pilot trial. J Trauma Acute Care Surg 2013, 75:657-663.
52 53	24		
54 55			
56 57			
58 59			18

1		
2 3		
4	1	FIGURES
5 6	2	
7 8	3	Figure 1
9 10	4	Figure legends: PRISMA flow diagram of the identification, screening, eligibility, and inclusion process
11 12	5	[14]. *One of the included studies [20] did not strictly meet the inclusion criteria, however, it is included for
13 14	6	descriptive purposes.
15 16	7	
17 18	8	
19 20 21	9	
21 22 23	10	
24 25	11	
26 27	12	
28 29	13	
30 31	14	
32 33	15	
34 35	16	
36 37	17	
38 39	18	
40 41	19 20	
42 43	20	
44 45	22	
46 47	23	
48 49	24	
50 51	25	
52 53	26	
54 55 56	27	
56 57 58		
58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 19

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

2 patients.

	Taher et a	al. [19]	Bazilay et a	I. [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 hyperoxia on clinical n outcomes of patients wi	eurological	" compare the results using ventilatory method, which combines HFPPV [high- frequency positive-pressure ventilation] a low-rate conventional mechanical ventilation (LRCMV), to the results using conventional mechanical ventilation (CM with PEEP." Not reported Interventional, non-randomized		
Blinding	Double blinded				
Study design	Randomized controlled	trial			
Inclusion criteria	Age 18-65 years; <6 hours passed since		All patients admitted to the ICU with a		
	the accident; hemodyna 3-8	amic stability; GCS	diagnosis of severe respiratory insufficient 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	2 2.2 (1.2	
Age [years], mean (SD)	39.7 (14.1)	45.7 (13.3)	40.6 (22.45)	39.8 (18	
Female sex, no. (%)	9 (26.5)	11 (32.4)	Not reported	Not repo	
GCS on admission, mean (SD)	7.4 (0.79) 0.80	7.4 (0.89)			
FiO ₂ , mean (SD)		0.50	0.45†	0.	
PaO ₂ [mmHg], mean (SD)	Not reported	Not reported	89.91 +/- 10.24†	78.43 +/- 11.	
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 report	
ICU LOS [days]	9.4 (6.6)	11.4 (8.4)	Not reported	Not repo	
Days on mechanical ventilation, mean (SD)	Not reported	Not reported	4.2 (0.91)	6.1 (

*†*during first 48 hours in hospital (FiO₂ estimated from other results)

5 Intensive Care Unit (ICU); Positive end expiratory pressure (PEEP); Traumatic brain injury (TBI); Glasgow Coma

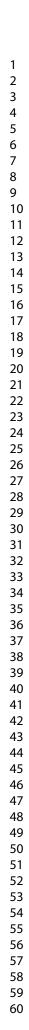
6 Scale Score (GCS); Cardio pulmonary resuscitation (CPR); Standard deviation (SD); inspiratory oxygen fraction

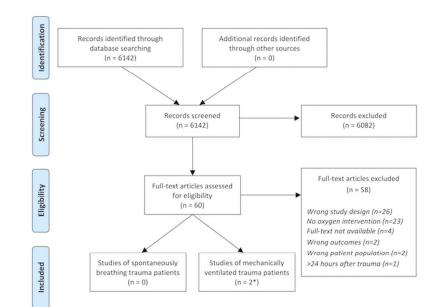
7 (FiO₂); arterial oxygen tension (PaO₂); Length of stay (LOS)

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	<i>Comment</i> : No description of a random component in th sequence generation process.	
Allocation concealment (selection bias)	Unclear	<i>Comment</i> : No description of allocation concealment.	High	Quote: "Patients were assigned alternately to two groups" Comment: Investigators ha the possibility of foreseein the assignment.	
Blinding of participants and personnel (performance bias)	Low	Quote: "In this double blind clinical trial" Comment: Probably done.	Low	<i>Comment</i> : 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	<i>Comment</i> : No blinding of outcome assessment is described, but the relevant outcomes are not likely to be influences by lack of blinding.	Low	<i>Comment</i> : 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	<i>Comment</i> : Outcome is reported for all included patients.	Unclear	Comment: The outcomes are not described as being defined before commencir the study.	
Selective reporting (reporting bias)	Unclear	<i>Comment</i> : No protocol is available and the reported outcomes are not pre- specified in the methods section.	Unclear	<i>Comment</i> : As outcomes are not described as being defined before commencir the study, there is insufficient information to assess this domain.	
Other bias	Unclear	<i>Comment</i> : 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.	

3 *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. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	7



PRISMA 2009 Checklist

Page 1 of 2

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			

41 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. 42 doi:10.1371/journal.pmed1000097 For more information, visit: www.prisma-statement.org.

Page 2 of 2 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

43

44

45