ACUTE TOXICITY THRESHOLD OF NORMOBARIC OXYGEN THERAPY: SYSTEMATIC REVIEW

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Abstract

Although there is clear dose-dependence of pulmonary toxicity caused by inhalation of normobaric oxygen in animal studies, the threshold of toxicity in humans remains mostly unknown. The aim of this systematic review of published clinical studies was to establish a threshold in terms of total oxygen dose administered under normal pressure by inhalation that causes the first clinical signs of toxicity. MEDLINE, EBSCO, The Cochrane Central Register of Controlled Trials (Central), SCIndex, Scopus, Google Scholar, and Clinical Trials.gov where searched from their foundation to April 2022. The systematic review was performed according to the pre-registered protocol at "PROSPERO". The studies were included if describing the toxic effects of normobaric oxygen therapy in humans. In total 11 human studies of poor quality were found, with either experimental or observational design. In none of the analyzed studies did oxygen therapy cause toxic effects on the respiratory tract if the concentration of oxygen in the inhaled air was below 50%, regardless of the rate of administration. The toxic consequences of inhaling oxygen at a concentration of more than 50% occurred only after oxygen was administered for more than 6 hours, at a rate of more than 7 L/min, and were mainly reflected in inflammation of the tracheobronchial mucosa, with epithelial erosions. In conclusion, normobaric oxygen therapy can have toxic effects on humans if the oxygen concentration in the inhaled air is higher than 50%, if the administration rate is above 7 L/min, and if the application lasts at least 6 hours.

Keywords: normobaric oxygen therapy, toxicity threshold, humans, systematic review

Introduction

Inhalation oxygen therapy is frequently given to hospitalized patients (35.2% of non-intubated patients have it), but in almost two-thirds of cases concentration and dose of oxygen were not prescribed by a physician[1]. However, if oxygen therapy is given without paying attention to the optimal dosing regimen, patients who receive it have more chances to die (relative risk is 1.21)[2]. Certain degrees of administered oxygen will always be transformed into free radicals (hydroxyl ion, peroxynitrite, superoxide anion, etc.), but with low dosage created radicals are neutralized by the body's antioxidative mechanisms. If large doses of concentrated oxygen are administered, the antioxidative mechanisms will be overwhelmed, and free radicals in excess will damage many functional proteins, disturbing the normal function of the respiratory tract in the first place[3]. After tracheobronchial irritation, atelectasis and alveolar damage may follow, up to the acute respiratory distress syndrome[3].

Although there is clear dose-dependence of pulmonary toxicity caused by inhalation of normobaric oxygen in animal studies, the threshold of toxicity in humans remains largely unknown[4]. The threshold will probably depend on the primary pulmonary pathology and therapy a patient receives since many drugs have antioxidant or anti-inflammatory properties[5]. While some guideline exists considering when to initiate and stop inhalation oxygen therapy according to

peripheral oxygen saturation (below 88% and above 92% in patients with risk factors for oxygen-induced hypercapnia, or below 92% and above 96% in patients without risk factors), there is no consensus about threshold dose of inhaled oxygen (concentration in a gas mixture delivered to the face mask or nasal catheter, volume of administered gas mixture/time of administration) that would induce first toxic changes in respiratory tract tissues[6], and this is not of less importance when a clinician has to prescribe inhalation oxygen therapy.

The aim of this systematic review of published clinical studies was to establish threshold in the terms of total oxygen dose administered under normal pressure by inhalation that causes the first clinical signs of toxicity.

Methods

This systematic review was pre-registered at the International prospective register of systematic reviews "PROSPERO" under the number CRD42021285512.

The studies were included in this systematic review if the following criteria were satisfied: patients of any race, age, and sex receiving normobaric inhalation oxygen therapy, at any dose regimen, for any indication, having toxic effects of inhalation oxygen therapy with onset of toxicity symptoms after initiation of inhalation oxygen therapy, and reporting results from clinical trials, observational studies or individual cases including case series. The exclusion criteria were: patients on mechanical ventilation, cases of toxicity of inhalation oxygen therapy mentioned in review articles, without detailed description, cases of inhalational oxygen therapy toxicity in non-human species, published cases or studies with incomplete data, and cases of hyperbaric oxygen therapy toxicity.

Relevant studies were searched for in electronic databases and a collection of books and journal articles at the University Library, University of Kragujevac, Kragujevac, Serbia. The following databases were searched: MEDLINE (Pubmed coverage from 1966 to present), EBSCO (Discovery Service, coverage from 1944 to present), The Cochrane Central Register of Controlled Trials (Central) (Wiley Online Library, coverage from 1966 to present), SCIndex, Scopus, Google Scholar and Registry of clinical studies with human participants, and ClinicalTrials.gov up to May 11, 2022). Electronic databases were searched for relevant studies by five authors independently: MJ, SM, EB, NO, and AA. The search strategy prepared by the MJ for the MEDLINE database is presented here as an example:

The studies relevant to this review were selected from the search results applying the inclusion and exclusion criteria at first on the title and abstract, and if it was ambiguous, the full text of the paper was read and analyzed. If all authors who searched (MJ, SM,EB, NO, and AA) agreed upon the inclusion of certain papers, it would be further processed. If the eligibility of a study was not agreed upon by all investigators who searched (MJ, SM, EB, NO and AA), senior authors (SJ and RV) made the final decision by consensus.

The studies selected, based on inclusion and exclusion criteria were further analyzed by applying quality criteria: modified Jadad scale for clinical trials[7], Newcastle Ottawa scale for observational studies[8], and Hassan Murad's tool for case series and case reports[9]. The scores according to these scales were determined for all selected studies and then taken into account for discussing the data.

The data from articles eligible for review after quality check were extracted to an Excel table with the following columns: (1) Publication ID; (2) Report ID; (3) Review author initials; (4) Citation and contact details; (5) Score according to a quality check scale; (6) Study design; (7) Total study duration; (8) Risk of bias; (9) Total number of patients; (10) Age of patients; (11) Sex of patients; (12) Concentration of oxygen delivered to a patient in inhaled air; (13) Dose of delivered oxygen in L/min; (14) Duration of oxygen therapy per 24h; (15) Total duration of oxygen therapy in days; (16) Indication for oxygen therapy (main disease of the patient); (17) Symptoms of oxygen toxicity; (18) Signs of oxygen toxicity; (19) Partial pressure of oxygen in arterial blood (in mmHg or kPa); (20) Level of free oxygen radicals in blood or other tissues; (21) Treatment of oxygen toxicity; (22) Outcome of treating oxygen toxicity; (23) Mortality of patients exposed to toxic doses of oxygen; (24) Whether acute respiratory distress syndrome was described as consequence of oxygen toxicity; (25) Emergence of pneumonia after onset of oxygen therapy; (26) Signs of oxygen toxicity at chest X-ray. Values provided as percentages were converted into actual patient numbers for analysis. The data were extracted by four researchers independently (MJ, SM, EB, andNO) and assembled in the final extraction table by two investigators (MJ and AA). Supervision of the extraction process was carried out by SJ and RV.

Assessment of risk of bias in the included studies

The risk of bias was assessed by four investigators independently (MJ, SM, EB, and NO), and the chief investigator (SJ) made the final evaluation. The following sources of bias were assessed: (1) reporting bias, (2) attrition bias, (3) selection bias (only if a clinical trial was reported), (4) performance bias (only if a clinical trial was reported), (5) reference bias, multiple publication bias and multiply used subject bias, (6) selector bias, (7) extractor bias, (8) quality assessment bias, and (9) detection bias (only if a clinical trial

Table 1. Summary of clinical studies assessing toxicity of normobaric inhalation oxygen therapy

STUDY	DESIGN	POPULATION	AGE AND SEX OF THE PATIENTS ACROSS TREATMENT GROUPS	CONCENTRATION OF NORMOBARIC OXYGEN, FLOW AND DURATION OF THERAPY	QUALITY OF THE STUDY (SCALE USED AND GRADE)
Vonbank et al, 2003	Randomized clinical trial	Patients with chronic obstructive pulmonary disease (COPD) (n=40)	Oxygen alone group (61.2±8.7 years, 6f:14m) Oxygen + nitric oxyde group (62.0±7.6 years, 7f:13m)	Concentration not reported, 4 L/min, 3 months	Jadad grade 5
Rockswold et al, 2010	Randomized clinical trial	Patients with traumatic brain injury (n=69)	Normobaric oxygen group (37 years, 4f:17m) Hyperbaric oxygen group (34 years, 3f:23m) and Control group (36 years, 4f:18m)	100% FiO_2, flow not reported, 3 hours daily for 3 days	Jadad grade 5
Caspersen et al, 2013	Crossover clinical trial with randomized exposure sequence	Healthy volunteers (n=18)	All patients exposed to 100% oxygen or ambient air, 24.0 ± 2.0 years, 10f:8m (37 years, 4f:17m)	100% FiO_2, 90 minutes	Jadad grade 4
Foschino Barbaro et al, 2005	Randomized clinical trial	Patients with chronic obstructive pulmonary disease (COPD)(n=45) and healthy volunteers (n=15)	COPD patients, all males, 62.8 ± 2.5 years, healthy controls, all males, 61.2 ± 3.8 years	24% FiO_2, 2 L/min, 18h continuously through nasal prongs	Jadad grade 4
Ackerman et al, 1988	Case report	A child with partial monosomy 21, exposed to oxygen during surgery	Twenty-six months old child, sex not reported	100% FiO_2, 4.5 hours	Hassan Murad scale, grade 7
Van De Water et al, 1970	Clinical trial	Healthy volunteers (n=11)	Males, 21-26 years old, 9 exposed to oxygen, 2 exposed to ambient air	100% FiO_2, 45 L/min, 1 day	Jadad grade 3
Sackner et al, 1975	Clinical trial	Healthy volunteers (n=10)	Average age 27 years (18-45 years), 8m:2f	90-95% FiO_2, 6 hours	Jadad grade 3
Comroe et al, 1945	Clinical trial	Healthy volunteers (n=90)	All males, aged between 19 and 31 years	Six volunteers were exposed for 24 h to 100% FiO_2 under the hood, and 28 volunteers were over the face mask; the control group of 10 volunteers was breathing compressed air over the face mask for 24 h; 9 volunteers were breathing 75% FiO_2 for 24 h, and 10 volunteers 50% FiO_2 for 24 h; 6 volunteers were exposed to 100% FiO_2 at half of the atmospheric pressure for 24 h, and 21 volunteers were exposed for 24 h to 100% FiO_2, with 1.5 or 15 minutes intermissions every 3 h	Jadad grade 4
Davis et al, 1983	Clinical trial	Healthy volunteers (n=16)	One group, 23.0 ± 1.1 years, 10m:6f	All patients were exposed to ambient air and then to 95% oxygen, 10-15 L/min for 18 h	Jadad grade 3
Montgomery et al, 1989	Clinical trial	Healthy volunteers (n=6)	One group, 22 ± 2 years of age, 4f:2m	All patients breathed 21%, 40%, and 100% oxygen, 14 L/min for 17 h, a week apart	Jadad grade 3
Pratt, 1958	Case series	A postmortem study of patients exposed to 100% oxygen (n=10)	Age from 57 to 80 years, 2f:8m	Exposed to 100% FiO_2, 4-7 L/min, for 1–19 days	Hassan Murad scale, grade 5

was reported). Reporting and attrition bias was evaluated in the first place for each study separately, checking what percentage of target outcomes was reported or what percentage of the patients withdrew from the study, respectively. The bias within this systematic review was avoided in the following ways: (1) selector bias was avoided by defining the criteria of selection from the beginning; (2) extractor bias was avoided by performing two separate readings and by resolving discordant evaluations; (3) quality assessment bias was avoided by defining the scoring systems from the beginning.

The study variables

The following variables were categorical: risk of bias, sex of patients, indication for oxygen therapy (main disease of the patient), symptoms of oxygen toxicity, signs of oxygen toxicity, treatment of oxygen toxicity, the outcome of treating oxygen toxicity, mortality of patients exposed to toxic doses of oxygen, whether acute respiratory distress syndrome was described as a consequence of oxygen toxicity, the emergence of pneumonia after the onset of oxygen therapy, and signs of oxygen toxicity at chest X-ray. The following variables used in the study were continuous: score according to a quality check scale, total study duration, the total number of patients, age of patients, the concentration of oxygen delivered to a patient in inhaled air, the dose of delivered oxygen in L/min, duration of oxygen therapy per 24 h, total duration of oxygen therapy in days, partial pressure of oxygen in arterial blood (in mmHg or kPa), and level of free oxygen radicals in blood or other tissues. In this systematic

review, individual patients extracted from the retrieved studies were units of analysis.

Missing data were requested from the authors of the original paper and recalled from the results presented on clinicalTtial.gov, if available. The influence of missing data was mentioned in the "Discussion section".

Assessment of heterogeneity did not apply to this type of systematic review. No clinical trial was found for quantitative data synthesis; narrative summation and tabulation of findings from individual publications were made.

Statistics

The data were described by mean and standard deviation, if continuous, and by frequencies and percentages, if categorical. Suitable graphs were used for better visualization of the data. The data processing was made by Microsoft Excel software, version 2019.

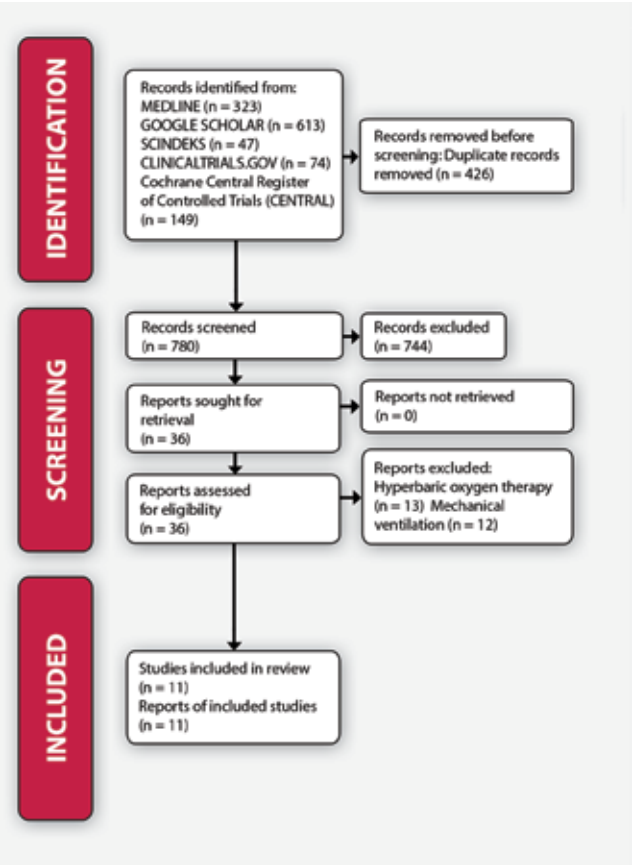
Results

After searching the databases, identifying the records, screening, and eligibility checking in total 11 published studies were included in the review; the selection process is presented in the Flow diagram (figure 1) built according to PRISMA recommendations[10]. Characteristics of the included studies are shown in table 1[11-21]. In total 331 human subjects were exposed to normobaric oxygen therapy in those 11 studies, all of them being adults, except one child. A little more than half of the adult subjects (n=166) were healthy volunteers, while the rest were patients (n=165), mostly with chronic obstructive pulmonary disease or brain trauma (the only child among patients was one suffering from partial monosomy[21]). Adverse outcomes of the normobaric inhalation oxygen administration were evaluated clinically, radiographically, by functional diagnostics, and/or by laboratory measurements. The main outcomes of exposure to normobaric oxygen in the included studies and assessment of the risk of bias are shown in table 2.

Only two of the analyzed studies explicitly reported partial pressure of oxygen in arterial blood when normobaric inhalation therapy with 100% oxygen (FiO_2 100%) was used; one study (n=6, healthy volunteers)[20] reported 459 mmHg and another (n=11, healthy volunteers)[16] reported 485-562 mmHg.

Two studies reported on oxidative stress induced by normobaric oxygen inhalation therapy. In the study on patients with traumatic brain injury (n=21)[12] levels of isoprostane in cerebrospinal fluid were not increased after normobaric oxygen therapy. On the other hand, when patients with Chronic Obstructive Pulmonary Disease (COPD)[14] were exposed to normobaric oxygen inhalation therapy glutathione disulfide and protein carbonyl groups significantly increased in erythrocytes (the latter also in plasma), while glutathione levels decreased; after stopping oxygen therapy levels of these markers of oxidative stress gradually were normalized. None of the studies reported death among patients or healthy volunteers exposed to normobaric inhalation oxygen therapy.

Image 1. Flowchart illustrating the identification and selection of studies for inclusion in the review



Five of 11 studies reported symptoms and signs of normobaric oxygen toxicity, but only when FiO_2 was 100% or 75%, and the rate of administration was > 7 L/min for more than 6 hours; no respiratory tract toxicity was noted when FiO_2 was below 50%. The main symptoms of oxygen toxicity were substernal discomfort, retrosternal pain, nasal congestion and coryza, sore throat, cough, and ear discomfort. The main signs of oxygen toxicity were tracheal edema, erosions, and excessive secretion, while vital capacity was reduced. Postmortem examination of patients exposed to normobaric oxygen therapy showed pulmonary capillary proliferation and thickening of alveolar septa in half of the exposed subjects.

Discussion

Although normobaric administration of oxygen via the respiratory tract is performed on millions of patients worldwide every day, there are surprisingly few clinical studies that have directly addressed the threshold dose of oxygen above which the first signs of toxicity appear. In our

Table 2. The outcomes of studies assessing toxicity of normobaric inhalation oxygen therapy and risk of bias

Study	Symptoms of oxygen toxicity	Clinical signs of oxygen toxicity	Radiographic signs of oxygen toxicity	Pneumonia or ARDS as a complication of oxygen therapy	A high risk of bias								
					Randomization	Sequence generation	Sequence concealment	Blinding	Selector bias	Extractor bias	Selective reporting	Follow-up-time bias	Attrition bias
Vonbank et al, 2003	None	None	None	None			✓	✓					
Rockswold et al, 2010	None	None	Two of the 21 pts on NBO had consolidation of lung tissue	Incidence not increased				✓					
Caspersen et al, 2013	None	None	None	None	✓	✓	✓	✓					✓
Foschino Barbaro et al, 2005	None	None	Not reported	None			✓	✓					
Ackerman et al, 1988	Not reported	Pulmonary edema	Bilateral pulmonary edema	Not reported	N/A*	N/A	N/A	N/A				✓	
Van De Water et al, 1970	No respiratory symptoms, irritation of eyes after 6-11 h	None	None	Not reported	✓		✓	✓					
Sackner et al, 1975	No substernal discomfort, 2 of 10 patients had symptoms of bronchitis	Redness and edema of the trachea in all patients, tracheal erosions in 3 of 10 patients, and excessive secretion in 5 of 10 patients	Not reported	Not reported	✓		✓	✓					
Comroe et al, 1945	95% of those inhaling 100% O_2 and 50% of those on 75% O_2 had substernal distress after 14 h on average; 43% on 100% O_2 developed nasal congestion and coryza, 32% sore throat, and 54% cough. 23% on 100% O_2 had conjunctival irritation and 25% ear discomfort. Those inhaling 50% oxygen had no symptoms.	79% of patients inhaling 50%. 75% or 100% O_2 developed a decrease in the vital capacity of the lungs; 25% had fatigue, 15% had joint pain, 9% had paresthesias.	None	None	✓	✓	✓	✓					
Davis et al, 1983	Substernal discomfort in 9 of 14 subjects	Mild erythema of tracheal and bronchial mucosa in 6 of 14 subjects	Not reported	Not reported	✓	✓	✓	✓					
Montgomery et al, 1989	Retrosternal pain when inhaling 100% O_2 after 9 hours	Not reported	Not reported	Not reported		✓	✓	✓					
Pratt, 1958	N/A – postmortem study	Pulmonary capillary proliferation and thickening of alveolar septa in 4 of 8 subjects	Pneumonia in 1 of 8 subjects	Not reported	✓	N/A	N/A	N/A	✓		✓	✓	

Abbreviaton: * N/A – not applicable

systematic review, we found 11 human studies, only a few of which fell into the randomized clinical study category, and were of poor quality. In none of the analyzed studies did oxygen therapy cause toxic effects on the respiratory tract if the concentration of oxygen in the inhaled air was less than 50%, regardless of the rate of administration. The toxic consequences of inhaling oxygen at a concentration of more than 50% occurred only after oxygen was administered for more than 6 hours, at a rate of more than 7 L/min, and were mainly reflected in inflammation of the tracheobronchial mucosa, with epithelial erosions. Alveolar damage resulting in pneumonia or acute respiratory distress syndrome has not been documented with certainty.

Due to the exposure of tissues to a high concentration of oxygen, a superoxide anion is formed by the electron transfer system in mitochondria, which easily builds a peroxynitrite ion with nitrogen monoxide[22]. Both free radicals (superoxide anion and peroxynitrite ion) directly disrupt the functioning of many cellular enzymes, which can turn into a visible toxic effect if the capacity of superoxide dismutase (converts superoxide to hydrogen peroxide), catalase, and glutathione peroxidase (these last two enzymes break down hydrogen peroxide) is overcome which coincides with the consumption of glutathione and its conversion into glutathione disulfide[22]. Tissue damage due to free radicals during normobaric oxygen therapy is greatest in the respiratory tract, where the concentration of oxygen is highest, and thus most free radicals are created. However, since oxygen

penetrates from the lungs directly into the bloodstream, free radicals are formed in other tissues as well. Two small studies on patients with either COPD or traumatic brain injury showed that during the administration of normobaric oxygen by inhalation free radicals are formed in the blood and cerebrospinal fluid, too, causing oxidative stress and decreasing levels of glutathione[12, 14]. However, symptoms and signs of oxygen toxicity in remote tissues were reported in only one, rather old and small study on healthy volunteers, and were limited to fatigue, joint pain, and paresthesia in up to a quarter of exposed subjects[18].

The key question from the clinical aspect remains whether normobaric oxygen therapy can, if applied in higher doses, do more harm than good, ie. to predispose the patient to nosocomial pneumonia or acute respiratory distress syndrome (ARDS). In the analyzed studies, such a connection has not been confirmed, but animal studies indicate that something like this could happen. Exposure of newborn rats to 95% oxygen under normal pressure for three days shortens the life of alveolar macrophages and reduces their phagocytic capacity[23]. Adult rats that inhale pure oxygen under normal pressure for 48 hours develop pulmonary edema and dyspnea, while biochemical analyzes show that endothelial cells in the lungs lose their integrity[24]. In another study, adult rats were exposed to 95% oxygen under normal pressure for 24 hours; after that period, severe congestion of the lung parenchyma was observed with the accumulation of fluid and erythrocytes in the alveoli, which did not subside even after 2 weeks after discontinuation of oxygen[25]. To determine whether there is a link between high-dose normobaric oxygen therapy and the development of nosocomial pneumonia or ARDS, it is necessary to conduct carefully designed observational studies in patients treated with different doses of oxygen.

The main limitation of this systematic review is due to the small number and low quality of published clinical studies examining the toxicity of normobaric oxygen therapy administered without artificial ventilation. Studies have also been found to be older, most likely due to the increasing use of normobaric oxygen therapy along with artificial ventilation in critically ill patients in intensive care units in recent decades; with such dual therapy, it is not possible to determine which of the two factors contributes to possible poor treatment outcomes, so studies with artificial ventilation have not been considered.

Conclusion

Normobaric oxygen therapy can have toxic effects if the oxygen concentration in the inhaled air is higher than 50%, if the administration rate is above 7 L/min, and if the application lasts at least 6 hours. Toxic effects determined with certainty are reflected in inflammation and damage to the tracheobronchial mucosa, which patients feel as substernal discomfort. Additional observational studies are needed to determine whether normobaric oxygen therapy may damage the lung parenchyma and predispose it to nosocomial pneumonia or ARDS.

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