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Effects of intraoperative high *versus* low inspiratory oxygen fraction (FiO_2) on patient's outcome: a systematic review of evidence from the last 20 years

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ABSTRACT

Despite numerous studies, controversies about the best intraoperative FiO_2 remain. In 2016, the World Health Organization recommended that adult patients undergoing general anaesthesia should be ventilated intraoperatively with an 80% FiO_2 to reduce surgical site infection (SSI). However, several data suggest that hyperoxia could have adverse effects. In order to determine the potential effect of FiO_2 on SSI, we included in this systematic review 23 studies (among which 21 randomised controlled trials [RCT]) published between 1999 and 2020, comparing intraoperative high *versus* low FiO_2. Results were heterogeneous but most recent studies on one hand, and the largest RCTs on the other hand, reported no difference on the incidence of SSI regarding intraoperative FiO_2 during general anaesthesia. There was also no difference in the incidence of SSI depending of intraoperative FiO_2 in patients receiving regional anaesthesia. The review on secondary endpoints (respiratory and cardiovascular adverse events, postoperative nausea and vomiting, postoperative length-of-stay and mortality) also failed to support the use of high FiO_2. On the opposite, some data from follow-up analyses and registry studies suggested a possible negative effect of high intraoperative FiO_2 on long-term outcomes. In conclusion, the systematic administration of a high intraoperative FiO_2 in order to decrease SSI or improve other perioperative outcomes seems unjustified in the light of the evidence currently available in the literature.

Keywords: inspired oxygen fraction, FiO_2, surgical site infection, intraoperative oxygen, respiratory complications, mortality

INTRODUCTION

Oxygen is certainly the most commonly prescribed medication in anaesthesia, whether during general or regional anaesthesia, and from induction to hours after the end of surgery. For years, intraoperative high inspiratory oxygen fractions (FiO_2) have been used to prevent and treat hypoxemia caused by alveolar hypoventilation, decrease in functional residual capacity, second gas effect, atelectasis and ventilation-perfusion mismatch, which could occur during all phases of anaesthesia. The justification of high FiO_2 also lays in the hope to prevent hypoxemia and hypoxia when critical events such as unplanned extubation, hypovolaemic or haemorrhagic shock occur during the surgical procedure. In addition, oxygen therapy may have perioperative beneficial effects, as it has been reported that supplemental intraoperative oxygen could reduce the risk of surgical site infection (SSI), notably by facilitating neutrophils bacterial killing [1–5]. Another potential benefit is the reduction of postoperative nausea and vomiting (PONV) [6,7]. The complete mechanism remains unknown. One hypothesis is that supplemental oxygen improves oxygen partial pressure in ischemic intestinal tissue during abdominal surgery and decrease the release of serotonin [8]. Then, in 2016, WHO strongly recommended that “adult patients undergoing general anaesthesia with tracheal intubation for surgical procedures should receive an 80% fraction of inspired oxygen intraoperatively and, if feasible, in the immediate postoperative period for 2-6 h to reduce the risk of SSI” [9]. Nevertheless, several concerns have been raised about these guidelines and the potential adverse events associated with high FiO_2. Moreover, the poor quality of evidence of this recommendation has also been criticised [10–15].

Indeed, it is now acknowledged that oxygen cannot be considered as an inert component. Actually, the physiological and physiopathological roles of oxygen and, more generally of radical species, have been studied extensively in medicine. When oxygen is combined to a free electron, they form very unstable elements called “reactive oxygen species” (ROS). Initially, ROS have only been considered for their potential toxic effects as they induce oxidative reactions that may generate membrane, DNA or protein damages [16–18]. However, after Mc Cord and Fridovich's discovery of superoxide dismutase (SOD), it appeared that oxygen and ROS played a key part in cell signalling [19–21]. Thus, administration of intraoperative supplemental oxygen can be a double-edged sword. High FiO_2 at induction or during general anaesthesia promotes absorptive atelectasis over a few

minutes [22–26]. In pathologic state such as shock or ischemia-reperfusion, hyperoxia may increase ROS generation within mitochondria and if the redox homeostasis balance is disturbed, a pro-oxidant state could lead to cell injury [27–29]. Clinical evidences are in line with experimental findings as ROS metabolism seems to be implicated in the deleterious effects of ischemia-reperfusion following resuscitation from cardiac arrest and myocardial infarction [30–32]. Moreover, it is now advocated that oxygen therapy should carefully be prescribed in acutely ill patients as morbidity, and maybe mortality, seem linked to the amount of oxygen delivered [33]. Actually, it has been reported that acutely ill patients treated with conservative oxygen therapy may have a better outcome than those treated with a liberal oxygen strategy [34–36]. Finally, systemic and coronary vasoconstriction induced by hyperoxia may increase cardiovascular morbidity in high-risk patients [37,38].

Thus, the question of how and when oxygen should be delivered remains unresolved. There are pro (prevention of hypoxemia and hypoxia, decrease in the risk of SSI and PONV) and con (respiratory adverse events, increase in potential harmful ROS production) arguments to administer intraoperative high FiO_2. Consequently, intraoperative administration of oxygen is very dependent on each practitioner and varies widely in clinical practice. This has been well illustrated in a study published in 2018 across 29 hospitals in the United Kingdom. The authors reported that intraoperative FiO_2 ranged from 25 to 100%, with a median FiO_2 of 50% regardless of patient's requirements. Arterial oxygen partial pressure (PaO_2) was supra-physiological (> 100 mmHg) in 89% of the 378 patients [39].

The aim of this study was to assess the benefit-risk ratio of the intraoperative administration of high FiO_2 by performing a systematic review over the 20 last years.

MATERIALS AND METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [40]. The PRISMA checklist is available as a supplementary file.

1. Search strategy

A search was conducted from the 1st of January 1999 to the 1st of February 2020 in MEDLINE (PubMed), CENTRAL (Cochrane) and ClinicalTrials.gov databases. The last search was conducted on the 1st of March 2020. There was no restriction on the type of the study. The following keywords were used: “perioperative”, “intraoperative”, “preoperative”, “postoperative”, “oxygen”, “supplemental oxygen”, “oxygenation”, “oxygen therapy”, “oxygen inhalation therapy”, “hypoxia”, “hyperoxia”, “FiO2”, “FiO(2)”, “inspired oxygen fraction”, “oxygen inhaled fraction”, “oxygen concentration”, “oxygen administration”, “oxygen dosage”, “anaesthesia”, “adverse effects”, “adverse events”, “outcomes”, “surgical site infection”, “postoperative wound infection”, “nausea and vomiting”, “PONV” (postoperative nausea and vomiting), “atelectasis”, “pulmonary complications”, “respiratory complications”, “lung function”, “respiratory failure”, “residual functional capacity”, “acute myocardial infarction”, “myocardial injury after non-cardiac surgery”, “MINS” (myocardial injury after non-cardiac surgery), “length of stay”, “death”, “mortality”, “cancer”. Booleans operators “and”, “or” and “not” were applied. The PubMed “similar article” function was used to expand the search.

2. Study selection

Two authors (C.F. and M.G.) independently screened the titles and abstracts retrieved from the search for potential eligibility. To be considered for analysis, publications had to be written in English or in French. When the title and abstract indicated potential eligibility, the full-text article was analysed. Editorials, letters to the editor, animal studies and paediatrics studies were excluded from the analysis. The references of the selected articles were also screened to complete the search. The PRISMA flow diagram of study selection is presented in **Figure 1**.

3. Outcomes

According to the Grade of Recommendation, Assessment, Development and Evaluation (GRADE) methodology, a preliminary classification of outcomes has been made by 3 investigators (C.F, M.G and C.Q) before reviewing the evidence using a 1–9 numerical scale, in which outcomes rated from 1 to 3 were considered as "low importance outcomes," from 4 to 6 as "important but not critical outcomes," and from 7 to 9 as "critical outcomes" [41]. Consequently, the judgement criteria used in our literature review were rated as follows: main criterion = surgical site infection (importance 8); secondary criteria = mortality (importance 9), adverse respiratory events (importance 7), adverse cardiovascular events (importance 7), length of stay (importance 6) and incidence of PONV (importance 4).

4. Data extraction and analysis

For each study, a first reviewer extracted the following data: first author, year of publication, study location, type of study, population studied, type of surgery, primary and secondary outcomes selected, and main results. Potential confounding factors that may influence the selected outcomes (for example the perioperative use of antibiotics, the composition of the inspired gas mixture, etc.) were reported. A second reviewer checked independently the extracted data. In case of a discrepancy, a consensus decision was made between the two reviewers. Study sample size and the relevance of the research were considered at the level of each study. Then, the methodological quality of RCTs was rated with the Oxford quality scoring system [42]. The analysis was performed according to decreasing hierarchical prioritisation of data from meta-analyses of randomised controlled trials (RCTs) or individual RCTs to observational studies.

RESULTS

1. Surgical site infection

1.1 Characteristics of the included studies

The main characteristics of the studies included in the literature review concerning the outcome "surgical site infection" are summarised in **Table 1.** Twenty-nine studies were first included. However, 6 RCTs by Schietroma et al. were excluded from the analysis [43–48] because of the retraction of 2 RCTs due to the falsification of the statistics [45,46] and of another RCT [43] for plagiarism and similarities of data with those previously published by another group. In addition, the validity of the 3 non-retracted RCTs [44,47,48] is also being questioned, notably because all 6 RCTs of this group reported important differences in SSI incidence systematically in favour of the high FiO_2 group. Eventually, 23 studies, among which 21 RCTs, were included in this review. Fifteen out of these 21 RCTs compared high *versus* low FiO_2 during surgery in patients under general anaesthesia (n = 6,984 patients); while the 6 remaining concerned patients receiving loco-regional anaesthesia (n = 2184 patients). Their quality assessment is reported in **Figure 2**.

For surgeries performed under general anaesthesia, the main surgical procedure was abdominal surgery (exclusively for 12 and mixed with other surgeries for 2 out of the 15 RCTs; n = 5715 patients operated from abdominal surgery/6,984 patients operated under general anaesthesia). Among abdominal surgeries, major abdominal procedures represented the large majority of interventions (exclusively in 11 and mixed with minor surgeries in 3 out of the 14 RCTs including abdominal procedures; n = 5,179 patients operated from major abdominal surgery/5,715 patients operated from abdominal surgery). For surgeries performed under loco-regional anaesthesia, the surgical procedure was caesarean sections under epidural anaesthesia in the 6 RCTs.

Definitions of "SSI" used in the studies were the CDC definition (n = 10/21 RCTs) [49], the ASEPSIS definition (Additional treatment, Serous discharge, Erythema, Purulent discharge, Separation of deep tissues, Isolation of bacteria, and prolonged Stay in hospital > 14 days) (n = 4/21 RCTs) [50], or other trial-specific definitions (n = 7/21 RCTs). The evaluation of the occurrence of a SSI was performed at day 15 or 30 after surgery in most studies.

About the main confounding factors that may influence the incidence of SSI, the second gas (i.e. composing the gas mixture with oxygen) used was variable (nitrous oxide or nitrogen);

antibiotic prophylaxis was protocolised in all studies but the protocol was not always followed; mean body temperature was effectively maintained above 36 °C in only 10/21 RCTs (temperature was lower or not specified in the other studies); the total amount of fluid administered during the surgery was protocolised in only 4/21 RCTs; and only one study specified whether non-steroidal anti-inflammatory drugs were prescribed postoperatively. Duration of a systematic post-operative oxygen therapy varied from 0 to 72 hours.

1.2 Results of the studies performed during general anaesthesia

1.2.1 RCTs. Four RCTs reported a reduction in the incidence of SSI in the high FiO_2 group [51–54], 2 RCTs reported a reduction in the low FiO_2 group [55,56], and 9 RCTs reported no significant difference between the groups [57–65]. The 3 largest multicentre RCTs were the PROXI trial (n = 1386; 2009) [61], the trial performed by Kurz et al. (n = 555; 2015) [58], and the iPROVE-O_2 trial (n = 717; 2020) [65]. There was no difference in the incidence of SSI between the 80% and 30% FiO_2 groups neither in the PROXI trial (CDC definition of SSI within the first 15 postoperative days, no nitrous oxide, antibiotic prophylaxis protocolised and systematic postoperative epidural analgesia: 19.1% *vs* 20.1%; $p = 0.64$), nor in the Kurz et al.'s study (CDC definition of SSI within the first 30 postoperative days, no nitrous oxide, antibiotic prophylaxis protocolised: 15.8% *vs* 15.6%; $p = 1.0$), nor in the iPROVE-O_2 study (CDC definition of SSI within the first 7 postoperative days, no nitrous oxide, antibiotic prophylaxis protocolised: 8.9% vs. 9.4%; $p = 0.90$). The incidence of deep SSI was higher in the high FiO_2 group in Kurz study (7% *vs* 3%; $p = 0.033$).

Of note, the ENIGMA RCT by Myles et al. (n = 2012; 2007) [52], that was included in most of the meta-analyses on this topic including the one that served to formalise the 2016 WHO recommendations [66], reported a reduction of SSI (secondary outcome) in the high vs. low FiO_2 group (7.7% *vs* 10%; OR 0.72 95%CI [0.53-0.98]; $p = 0.034$). However, the first aim of this study was to assess the effect of nitrous oxide avoidance, leading to a high FiO_2 group ventilated without N_2O (80% O_2/20% N_2) and a low FiO_2 group ventilated with 70% N_20/30% O_2.

1.2.2 Non-randomised studies. Kurz et al. performed a large cluster cross-over randomised trial in which the FiO_2 was set alternately at 30% and 80% biweekly for all the patients undergoing colorectal surgery [67]. From 2013 to 2016, 5749 patients were followed. The

incidence of the composite primary endpoint (SSI, wound complication and 30-day surgical mortality) was similar between the 2 groups (10.8% *vs* 11% in the high and low FiO_2 groups, respectively; RR 0.99 [0.85-1.14]; *p* = 0.85). There was also no between-group difference regarding the "SSI" outcome alone (4.1% *vs* 3.9%; RR 1.04 [0.74-1.46]; *p* = 0.77). Wanta et al. matched 1250 cases with 3248 controls who undergone abdominal, orthopaedic, vascular and neurosurgical surgeries, and found no association between increased oxygen exposure during surgery and the incidence of SSI in a multivariable logistic regression model [68].

1.3 Results of the studies performed during loco-regional anaesthesia

Six RCTs compared the incidence of SSI when administrating high or low FIO_2 during caesarean section. Three studies had used different oxygen delivery devices between the high (concentration mask) and low (nasal cannula) FiO_2 groups [69–71]. Only 2 studies specified the timing of antibiotic prophylaxis (at the time of cord clamping) [72,73]. The incidence of SSI varied from 1% [71] to 19% [72] depending on the studies. However, these 6 RCTs reported no significant difference between the high and low FiO_2 groups.

2. Secondary outcomes

2.1 Adverse respiratory events

The main characteristics of the studies included in the literature review concerning the outcome "adverse respiratory events" are summarised in the **Supplementary Table 1.** Eleven RCTs and 1 registry study were included.

2.1.1 Atelectasis

Of 9 RCTs, 6 reported no difference in the incidence of atelectasis [61,65,74–77]. Edmark et al. reported a significant but poorly relevant difference on the surface of atelectasis assessed by chest CT-scan performed just after the induction of anaesthesia between the 100% and 60% FiO_2 groups [25]. Similarly, Zoremba et al. reported fewer atelectasis in the 40% *vs* 80% FiO_2 groups up to 24 hours after surgery in 142 overweight patients (BMI = 25-35 kg/m^2), without any difference in SaO_2 [78]. Finally, Myles et al. reported more atelectasis in the FiO_2 30%/N_2O 70% compared to the FiO_2 80%/N_2 20% group (13% *vs* 7.5%; *p* < 0.001) [52].

2.1.2 Pneumonia

Of 3 RCTs, only Myles et al. [52] reported an increased incidence of postoperative pneumonia in the 30% compared to the 80% FiO_2 groups (3% *vs* 1.5%; $p = 0.031$). Both Chen et al. (n = 91) [57] and Staehr et al. (n = 213 obese patients from the PROXI cohort) [77] reported a similar incidence of pneumonia between the 30% and 80% FiO_2 groups (9% *vs* 3%, $p = 0.50$ and 4.5% *vs* 5.9%, $p = 0.65$; respectively) after abdominal surgery.

2.1.3 Composite respiratory outcome

In Myles' study, the incidence of the composite respiratory outcome (pneumonia, atelectasis, pneumothorax and pulmonary embolism) was decreased in the FiO_2 80%/N_2 20% group compared to the FiO_2 30%/N_2O 70% group (7.8% *vs* 13%; $p < 0.001$) [52]. By contrast, Ferrando et al. reported in the most recent study in which lung-protective ventilation and an open-lung approach were used, no difference concerning the incidence of the composite respiratory outcome (13.1% *vs* 15.2% in the 80% and 30% FiO_2 groups, respectively; $p = 0.50$) [65]. Finally, Staehr-Rye et al. reported a dose-dependent association between the incidence of major respiratory complications (respiratory failure, re-intubation, acute pulmonary oedema and pneumonia) and the increase in intra-operative median FiO_2 in a large prospective monocentric U.S. registry [79].

2.2 Adverse cardiovascular events

The main characteristics of the studies included in the literature review concerning the outcome "adverse cardiovascular events" are summarised in the **Supplementary Table 2.** Three RCTs, the 5-year post-hoc follow-up study of the PROXI cohort and a registry study were included.

The 3 RCTs reported no difference in the incidence of myocardial infarction within 30 days after surgery [52,57,65]. At longer follow-up, the post-hoc analysis of the PROXI study [61] reported an increased incidence of myocardial infarction in the 80% compared to the 30% FiO_2 groups (2.2% *vs* 0.9%; HR 2.86 [1.10-7.44]; $p = 0.03$) at a median follow-up period of 3.9 years after surgery [80]. Finally, no association was reported between intra-operative FiO_2 and the incidence of postoperative myocardial infarction in the registry study by Staehr-Rye et al. [79].

2.3 Postoperative Nausea and Vomiting

The main characteristics of the studies included in the literature review concerning the outcome "postoperative nausea and vomiting" are summarised in the **Supplementary Table 3**.

Twelve RCTs (n = 5656 patients) reported the incidence of PONV [6,7,52,63,81–87]. In great majority, the study population were women undergoing gynaecological, breast or abdominal surgery. Three RCTs reported a decreased incidence of PONV in the high FiO_2 group [6,7,52]. In the studies by Greif et al. (n = 231; 1999) [6] and Goll et al. [7] (n = 240; 2001), PONV incidence was halved in the 80% compared to the 30% FiO_2 group (17% *vs* 30%; $p = 0.03$ [6] - 22% *vs* 44%; $p = 0.003$ [7]). These two studies used inhaled anaesthesia with isoflurane, no intraoperative prevention of PONV and postoperative analgesia with piritramide without any loco-regional analgesia. Secondary outcomes such as time to oral re-feeding, hospital discharge, as well as patient satisfaction (measured by willingness to have the same anaesthesia for future surgery), were similar between groups. In the ENIGMA study, the incidence of PONV was lower in the N_2 20%/O_2 80% group compared to the N_2O 70%/O_2 30% group (10% *vs* 23%; $p < 0.001$ [52]). The other 9 RCTs (n = 3173) did not report any difference in the incidence of PONV depending on intraoperative FiO_2 [61,63,81–87]. In particular, the studies by Joris et al. (n = 150 thyroid surgeries, 2003) [81] and Turan et al. (n = 559 mixed surgeries > 1 h, 2006) [85] designed with PONV incidence as primary outcome, reported similar incidence of nausea (46% *vs* 48% and 26% *vs* 20%, respectively) and vomiting (22% *vs* 24% and 8% *vs* 9%, respectively) in the high *vs* low FiO_2 groups.

2.4 Length-of-stay

The main characteristics of the studies included in the literature review concerning the outcome "length-of-stay" are summarised in the **Supplementary Table 4**.

Nine RCTs and the Kurz cluster cross-over study reported the length-of-stay according to intraoperative FiO_2 [51–53,56,57,61,62,64,67,72]. Wasnik's study reported a decreased length-of-stay in the high FiO_2 group (7.4 ± 3.6 *vs* 9.8 ± 3.7 days; $p = 0.003$) [64]. The main objective of this Indian monocentric study (n = 64) was to compare intraoperative 80% *vs* 30% FiO_2 on the incidence of SSI after appendicectomy. By contrast, the largest RCT having reported length-of-stay as a secondary outcome, the PROXI RCT (n = 1386, abdominal surgery > 2 h) [61], reported similar length-of-stay in the 80% and 30% FiO_2 groups (6 (1-34)

vs 7 (2-36) days, respectively – p = 0.09). The 7 other studies also reported no difference in length-of-stay between the high and low FiO_2 groups.

2.5 Mortality

The main characteristics of the studies included in the literature review concerning the outcome "mortality" are summarised in the **Supplementary Table 5.** Eight RCTs and 3 observational studies reported the mortality rate after general anaesthesia.

None of the 5 RCTs reporting short-term mortality reported any between-group difference [53,57,58,61,65]. In addition, Staehr-Rye et al. analysed 73,922 anaesthetic procedures for non-cardiothoracic surgeries from a monocentric U.S. registry [79] and reported that the median FiO_2 during anaesthesia was associated in a dose-dependent manner with increased mortality at day 7 and day 30. For instance, the OR for mortality at day 30 when comparing patients from the higher quintile of FiO_2 to those from the lower quintile was 1.97 [1.30-2.99] ($p < 0.001$).

DISCUSSION

The objective of our systematic review was to determine the benefit-risk balance of using high FiO_2 in the operating theatre. Among the 23 studies (including 21 RCTs) comparing the effect of a high (80%) *versus* low (30%) FiO_2 on the incidence of SSI, results were heterogeneous. However, the most recent studies reported no difference on the incidence of SSI with high or low FiO_2 in patients undergoing general anaesthesia. The multicentre RCT PROXI published in 2009 [61], which was the second largest study (n = 1386) and had the best quality score (Oxford score 5/5), did not report any reduction of the incidence of SSI with the administration of 80% FiO_2 during colorectal surgery. Similarly, the recent multicentre RCT iPROVE-O_2 reported a similar SSI rate between the 30% and 80% FiO2 groups [65]. Conversely, the large ENIGMA study (n = 2012) [52] reported opposite results. Further, this study was the only study among the 23 considered in the analysis that reported a significant benefit of a high FiO_2 at the same time on the incidence of SSI, pneumonia, atelectasis, and postoperative nausea and vomiting. However, the main objective of this study was to evaluate the effects of nitrous oxide on the length-of-stay (primary outcome) and various secondary outcomes, such as SSI or respiratory complications, in patients undergoing major surgery. Therefore, randomisation affected patients in a nitrous oxide-free group (FiO_2 80%/N_2 20%) or nitrous oxide group (FiO_2 30%/N_2O 70%), in which inspired oxygen fraction varied accordingly. Thus, it is not strictly speaking a comparison between high and low FiO_2, since one group received a high inspired fraction of nitrous oxide and the other group did not receive any. This is a major source of interpretation bias, especially considering that nitrous oxide may compromise host defence mechanisms [57], favour atelectasis, and contribute to nausea and vomiting [90].

The meta-analysis performed by de Jonge et al. on studies from 1990 to 2018 [91], reported a significant reduction of the incidence of SSI in the high intraoperative FiO_2 group in intubated patients (RR 0.80 [0.64-0.99]). Clearly, the inclusion of Myles' study in the analysis, whose sample of 2012 patients represented more than one third of the total population included in the meta-analysis (weight of 17% in the result of the analysis in ventilated patients), had impacted the overall effect. However, the level of evidence of the meta-analysis, as assessed by the authors themselves, was only moderate, and the results rather weak. Along these lines, our review, which included the two recent studies published beyond the inclusion period of de Jonge's meta-analysis [59,65], did not show a real benefit

of high FiO_2. It should be recognised that the studies included in the meta-analysis by De Jonge and in our qualitative review, presented significant heterogeneity, which should lead to cautious interpretation of the results. Indeed, some studies had small samples < 100 patients [57,60,64] while others included more than 500 patients [52,53,58,61,65]. The incidence of SSI was also very different, from a few percent in some studies [57,63,67] to more than 20% in others [51,59,61]. This may be due to the definition of SSI that was used in each study. Indeed, the way in which SSI is defined directly impacts its incidence. In a prospective observational study [92], the incidence of "SSI" ranged in the same cohort from 6.8% to 19% when using the ASEPSIS score or the CDC definition to diagnose postoperative infection. In this context, it is questionable whether the comparison of results between studies not using the same SSI diagnostic criteria is relevant. The difference in incidence of SSI among the studies may also have been related to the different control of the confounding factors affecting the incidence of SSI, such as correct administration of antibiotic prophylaxis, perioperative maintenance of normothermia, etc. For instance, antibiotic prophylaxis was correctly administered to only 70% of the patients included in the large PROXI RCT [61]. Finally, the surgical site (abdominal *vs* extra-abdominal) and the surgical approach (laparotomy or laparoscopy) were variable among studies, while this is known to impact the incidence of SSI [93].

Eventually, we believe that the available literature does not support the conclusion that there is a sufficiently significant effect of high FiO_2 to recommend its systematic use to prevent SSI in patients who are mechanically ventilated in the operating theatre. This has been recently confirmed by the results of the large randomised iPROVE-O_2 trial, which used many of the current standards of perioperative management, at least in patients undergoing major abdominal surgery.

Considering patients operated under loco-regional anaesthesia, the results are more homogenous as the 6 available studies included caesarean sections and did not report any difference in the incidence of SSI between the high and low FiO_2 groups. This is confirmed in the meta-analysis by de Jonge et al. [91] that included 5 of the 6 studies we identified in this review with the exception of Admadé's study [70]. Thus, routine administration of supplemental oxygen to patients having caesarean section under epidural or spinal

anaesthesia could be strongly questioned, considering that it does not appear to impact neither maternal nor foetal prognosis [94].

Considering secondary outcomes, the theoretical beneficial effect of a high FiO_2 is no more reported than for SSI prevention. No advantage on short-term mortality was reported in RCTs. However, demonstrating any potential effect of intraoperative FiO_2 on mortality would require a very large sample of patients, hardly compatible with the conduct of a RCT, as perioperative mortality has become very low. In this context, large registry studies can provide relevant arguments. Along these lines, the study by Staehr-Rye et al. [79] analysed data from 73,922 patients and reported a striking association between high FiO_2 and increased mortality at 7 and 30 days. This result has to be confirmed in further studies before concluding that there is a real noxious effect of high intraoperative FiO_2 on postoperative survival. Nevertheless, this result draws attention to the fact that the safety of high FIO_2 may not be as clear-cut as it sounds. Moreover, the follow-up study of the PROXI cohort showed higher 2-year mortality in patients randomised in the 80% compared to the 30% FiO_2 group (23.2% *vs* 18.3% - $p = 0.03$; and 33.5% *vs* 24.6% for patients who undergone cancer surgeries – $p = 0.009$) [88]. This highlights the need to extend the monitoring and analysis period to long-term mortality in future studies, notably in carcinologic patients.
Finally, the results on respiratory adverse events were inconclusive. Due to the age of some studies, the intraoperative ventilatory parameters used in these studies did not follow current recommendations on perioperative protective ventilation: tidal volumes up to 10 ml/kg, no use of PEEP, absence of alveolar recruitment manoeuvres, and use of nitrous oxide. In the light of the progress made in the field of perioperative ventilation, these results seem difficult to transpose into current practice. This seems particularly true when taking into account the increasing proportion of ambulatory surgery and the rapid implementation of enhanced recovery measures after surgery. To confirm these words, the recent iPROVE-O_2 trial, which used a mechanical ventilation strategy following the most recent guidelines based on protective ventilation and open-lung approach during the entire duration of anaesthesia, did not report any difference in atelectasis and pulmonary complication rates between the 80% and 30% FiO_2 groups.

In conclusion, the systematic administration of a high intraoperative FiO_2 in order to reduce surgical site infections seems unjustified in the light of the evidence currently available in the literature. While evidence of toxicity of a high FiO_2 remains to be demonstrated, there is no evidence that high FiO_2 can improve postoperative patient's outcome on its own.

Table 1. Summary of the main characteristics and results of the studies included and analysed for the main outcome "SSI".

Study	Country	Design, n	Type of surgery, procedure duration	O_2 duration in recovery room	SSI definition, follow up	SSI, n (%)	Gas[1]	Antibiotic prophylaxis	Temp.[2]	Fluids	Analgesia
Greif et al. [53], 2000	Austria, Germany, USA	RCT Multicentric N = 500	Colorectal, 3.1 h	2 h	Wound infection (pus), Day 15	FiO_2 80%: 13/250 (5.2%) FiO_2 30%: 28/250 (11.2 %) *P* = 0.01	N_2	No [3]	Yes	15 ml/kg/h	*NA/NP*
Pryor et al. [56], 2004	USA	RCT Monocentric N = 160	Major abdominal laparotomy or laparoscopy, 3.5 h	2 h	Clinical and paraclinical requiring medical support, Day 14	FiO_2 80%: 20/80 (25%) FiO_2 35%: 9/80 (11.3 %) *P* = 0.02	N_2O	Yes	No	15 ml/kg/h	*NA/NP*
Belda et al. [51], 2005	Spain	RCT Multicentric N = 291	Colorectal laparotomy	6 h	CDC, Day 14	FiO_2 80%: 22/148 (14.9%) FiO_2 30%: 35/143 (24.4%) *P* = 0.04	Air	Yes	Yes	15 ml/kg/h	NSAID
Mayzler et al. [60], 2005	Israel	RCT Monocentric N = 38	Colorectal Carcinologic, 2.3 h	2 h	Wound infection, Day 30	FiO_2 80%: 2/19 (12.5%) FiO_2 30%: 3/19 (17.6%) *P* = 0.53	N_2, N_2O	Yes	*NA/NP*	15 ml/kg/h	PCA
Myles et al. [52] 2007	Australia	RCT Multicentric N = 2012	Major surgery > 2 h[i], 3.1 h	-	Wound infection (pus or positive culture), Day 30	FiO_2 80%: 77/997 (7.7%) FiO_2 30%: 106/1015 (10.4%) *P* = 0.034	N_2, N_2O	Yes	*NA/NP*	*NA/NP*	+/- Regional analgesia
Gardella et al. [72], 2008	USA	RCT Monocentric N = 143	Caesarean section under regional anaesthesia, 0.8 h	2 h	Endometritis or wound infection requiring ATB, Day 14	Mask 15 L/min: FiO_2 80%: 17/69 (25%) FiO_2 30%: 10/74 (14%) *P* = 0.13	Air	Yes (at cord clamp)	*NA/NP*	*NA/NP*	*NA/NP*
Meyhoff et al. [61], 2009	Denmark	RCT Multicentric N = 1386	Abdominal laparotomy, 2.2 h	2 h[4]	CDC, Day 14	FiO_2 80%: 131/685 (19.1%) FiO_2 30%: 141/701 (20.1%) *P* = 0.64	Air	Yes (70% of cases)	Yes	Restrictive	Perime-dullary block (70%)
Anthony et al. [55], 2011	USA	RCT Monocentric N = 197	Colorectal laparotomy or laparoscopy, 2.7 h	2 h[5]	CDC, Day 30	FiO_2 80%: 45/100 (45%) FiO_2 30%: 23/97 (24%) *P* = 0.003	*NA/NP*	Yes	Yes	*NA/NP*	*NA/NP*
Bickel et al. [54], 2011	Israel	RCT Monocentric N = 210	Appendectomy Mac Burney, 0.5 h	2 h	ASEPSIS, Day 14	FiO_2 80%: 6/107 (5.6%) FiO_2 30%: 14/103 (13.6%) *P* = 0.04	N_2 Air	Yes	Yes	*NA/NP*	*NA/NP*

Scifres et al. [69], 2011	USA	RCT Monocentric N = 585	Caesarean section under regional anaesthesia, 1 h	2 h[6]	Endometritis or wound infection, Day 30	10 L/min (FiO_2 80%): 35/288 (12.2%) 2 L/min (FiO_2 30%): 26/297 (8.8%) *P* =0.18	Air	Yes	*NA/NP*	*NA/NP*	*NA/NP*
Thibon et al. [63], 2012	France	RCT Multicentric N = 434	Abdominal laparoscopy/tomy + breast cancer surgery, 1.5 h	-	CDC, Day 30	FiO_2 80%: 15/226 (6.6%) FiO_2 30%: 15/208 (7.2%) *P* = 0.81	Air	Yes (51.5% of cases)	*NA/NP*	*NA/NP*	*NA/NP*
Admadé et al. [70], 2013	Panama	RCT Monocentric N = 343	Caesarean section under regional anaesthesia, -	2 h[8]	CDC Day 30	FiO_2 80%: 9/164 (5.5%) AA: 13/179 (7.3%) *P* = 0.33	Air	Yes	*NA/NP*	*NA/NP*	*NA/NP*
Chen et al. [57], 2013	Hong Kong	RCT Monocentric N = 91	Colorectal, 2.8 h	24 h[9]	CDC, Day 30	FiO_2 80% + N_2: 2/30 (6.7%) FiO_2 30% + N_2O: 2/30 (6.7%) FiO_2 30% + N_2: 6/31 (9.4%) *P* = 0.21	N_2 N_2O	Yes	Yes	*NA/NP*	PCA Perime-dullary block (15.5%)
Duggal et al. [95], 2013	USA	RCT Monocentric N = 831	Caesarean section under regional anaesthesia -	1 h	Endometritis or wound infection, Day 45	10 L/min (FiO_2 80%): 34/416 (8.2%) 10 L/min (FiO_2 30%): 34/415 (8.2%) *P* = 0.89	Air	Yes	*NA/NP*	*NA/NP*	*NA/NP*
Stall et al. [62], 2013	USA	RCT Monocentric N = 235	Orthopaedic trauma surgery[10], 3.8 h	2 h	CDC, Day 84	FiO_2 80%: 14/119[11] (12%) FiO_2 30 %: 19/116 (16%) *P* = 0.31	-	Yes	*NA/NP*	*NA/NP*	*NA/NP*
Williams et al. [73], 2013	USA	RCT Monocentre N = 160	Caesarean section under regional anaesthesia 0.9 h	2 h	CDC, endometritis, Day 42	FiO_2 80%: 10/77 (13.0%) FiO_2 30 %: 12/83 (14.5%) *P* = 0.82	Air	Yes (at cord clamp)	*NA/NP*	*NA/NP*	*NA/NP*
Kurz et al. [58], 2015	USA, Ireland, Austria	RCT Multicentric N = 555	Colectomy laparotomy > 2 h, 3.5 h	1 h	CDC, Day 30	FiO_2 80%: 45/285 (15.8%) FiO_2 30%: 42/270 (15.6%) *P* = 1.00	N_2	Yes	Yes	*NA/NP*	Perime-dullary block
Wasnik et al. [64], 2015	India	RCT Monocentric N = 64	Appendectomy Mac Burney, 1 h	2 h[13]	ASEPSIS, Day 14	FiO_2 80%: 0/32 FiO_2 30%: 0/32	*NA/NP*	Yes	Yes	*NA/NP*	*NA/NP*
Fariba et al. [71], 2016	Iran	RCT Monocentric N = 122	Caesarean section under regional anaesthesia, 1 h	6 h	ASEPSIS, Day 14	FiO_2 80%: 0/61 FiO_2 30%: 1/61 *P* > 0.05	*NA/NP*	*NA/NP*	*NA/NP*	*NA/NP*	*NA/NP*

Kurz et al. [67], 2018	USA	Interventional[14] Monocentric N = 5749	Major abdominal > 2 h laparotomy or laparoscopy		CDC, Day 30	FiO_2 80%: 118/2896 (4.1%) FiO_2 30%: 112/2853 (3.9%) *P* = 0.77	*NA/ NP*	Yes	Yes	*NA/NP*	Perime-dullary (10%) TAP (3%)
Wanta et al. [68], 2018	USA	Case-control Monocentric 1,250 cases 3,248 controls over 10 years	General, orthopaedic, vascular, neurologic surgeries	-	CDC, Day 30	No association between duration with FiO_2>50% (% of duration of the procedure) or nadir FIO_2 and SSI	*NA/ NP*	*NA/NP*	*NA/NP*	*NA/NP*	*NA/NP*
Mayank et al. [59], 2019	India	RCT Monocentric N = 94	Colorectal	6 h	ASEPSIS, Day 30	FiO_2 80%: 26/47 (55.3%) FiO_2 30%: 19/47 (40.4%) *P* = 0.21	N_2	*NA/NP*	*NA/NP*	*NA/NP*	*NA/NP*
Ferrando et al. [65] 2020	Spain	RCT Multicentric N = 717	Abdominal >2 h, 3.5 h	3 h	CDC Day 7 (main outcome) and day 30	FiO_2 80%: 31/362 (8.9%) FiO_2 30%: 34/355 (9.4%) *P* = 0.90 FiO_2 80%: 52/362 (16.5%) FiO_2 30%: 62/355 (19.9%) *P* = 0.89	Air	Yes (85% of cases)	*NA/NP*	*NA/NP*	Regional anaesthesia (44%)

O_2: oxygen, SSI: surgical site infection, n: number, Temp.: temperature, N_2: nitrogen, N_2O: nitrous oxide, AA: ambient air NSAID: non-steroidal anti-inflammatory drug, CDC: Centers for Disease Control and Prevention, PCA: patient controlled analgesia, TAP: Transverse abdominal plane block, NA/NP: non-available or non protocolised

[1] Carrier gas (air, N_2O or N_2)
[2] Mean body temperature at extubation ≥ 36 °C
[3] Empirical post-operative antibiotherapy
[4] FiO_2 80% : 14 L/min, FiO_2 30% : 2 L/min
[5] FiO_2 80% group.
[6] FiO_2 80%: 2L/min, FiO_2 25-30%: 10 L/min
[7] Post-operative O_2 group: FiO_2 30% at day 0 and day 1 then O_2 5 L/min until day 2
[8] FiO_2 80% group
[9] FiO_2 80% or 30%
[10] Tibial plateau, tibial pilon, and calcaneus fractures
[11] Fractures
[12] During 16 hours postoperatively
[13] FiO_2 80% group
[14] FiO_2 was alternated between 30% and 80% at 2-week intervals for 39 months

Figure legends

Figure 1: Flow diagram of study selection for the assessment of the primary outcome (surgical site infection).

Figure 2: Oxford quality scoring system of the 23 RCTs included for the assessment of the primary outcome (surgical site infection).

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measured outcome, observational period or site of surgery? Anaesthesia 2006;61:628–33. https://doi.org/10.1111/j.1365-2044.2006.04703.x.
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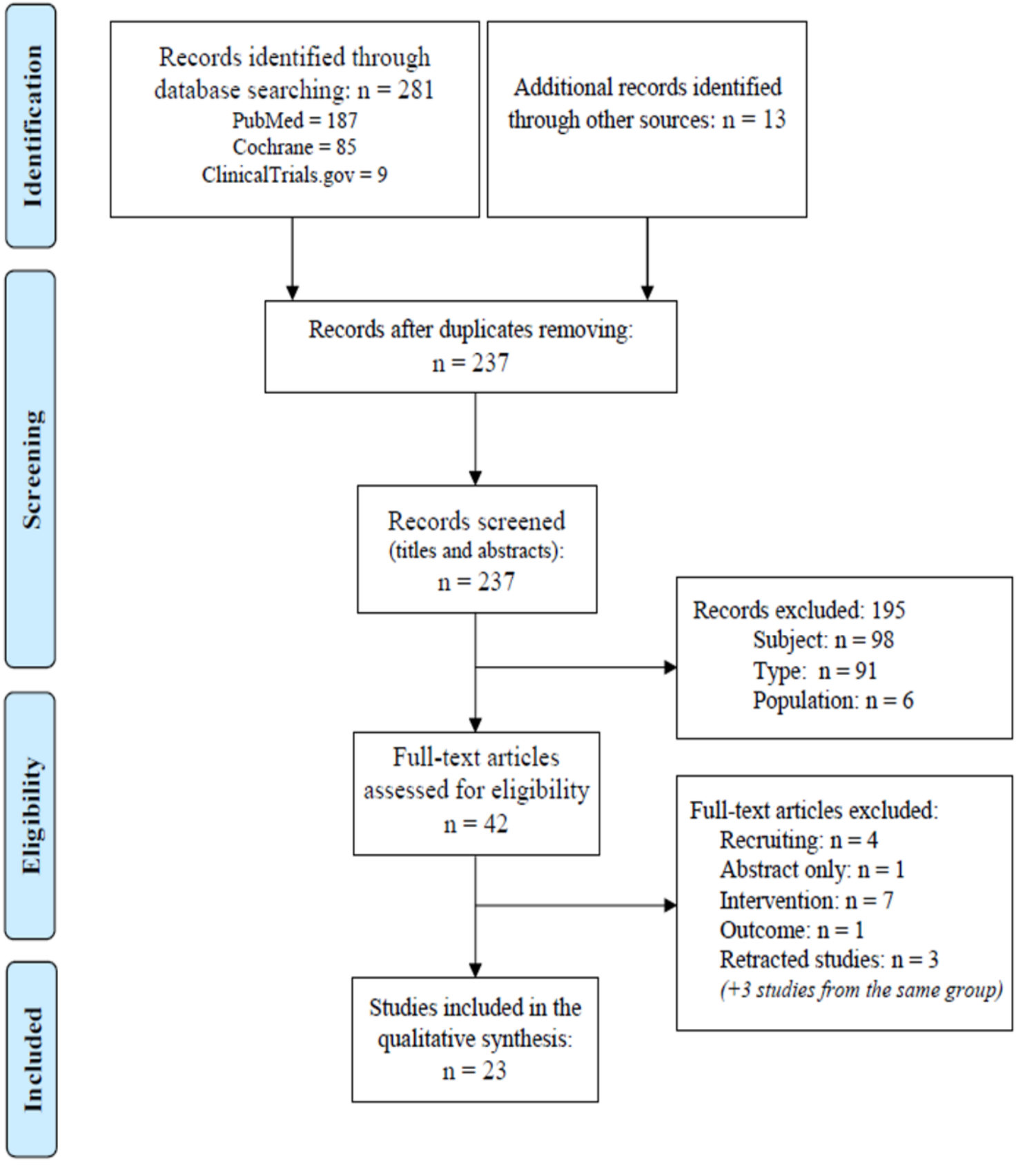
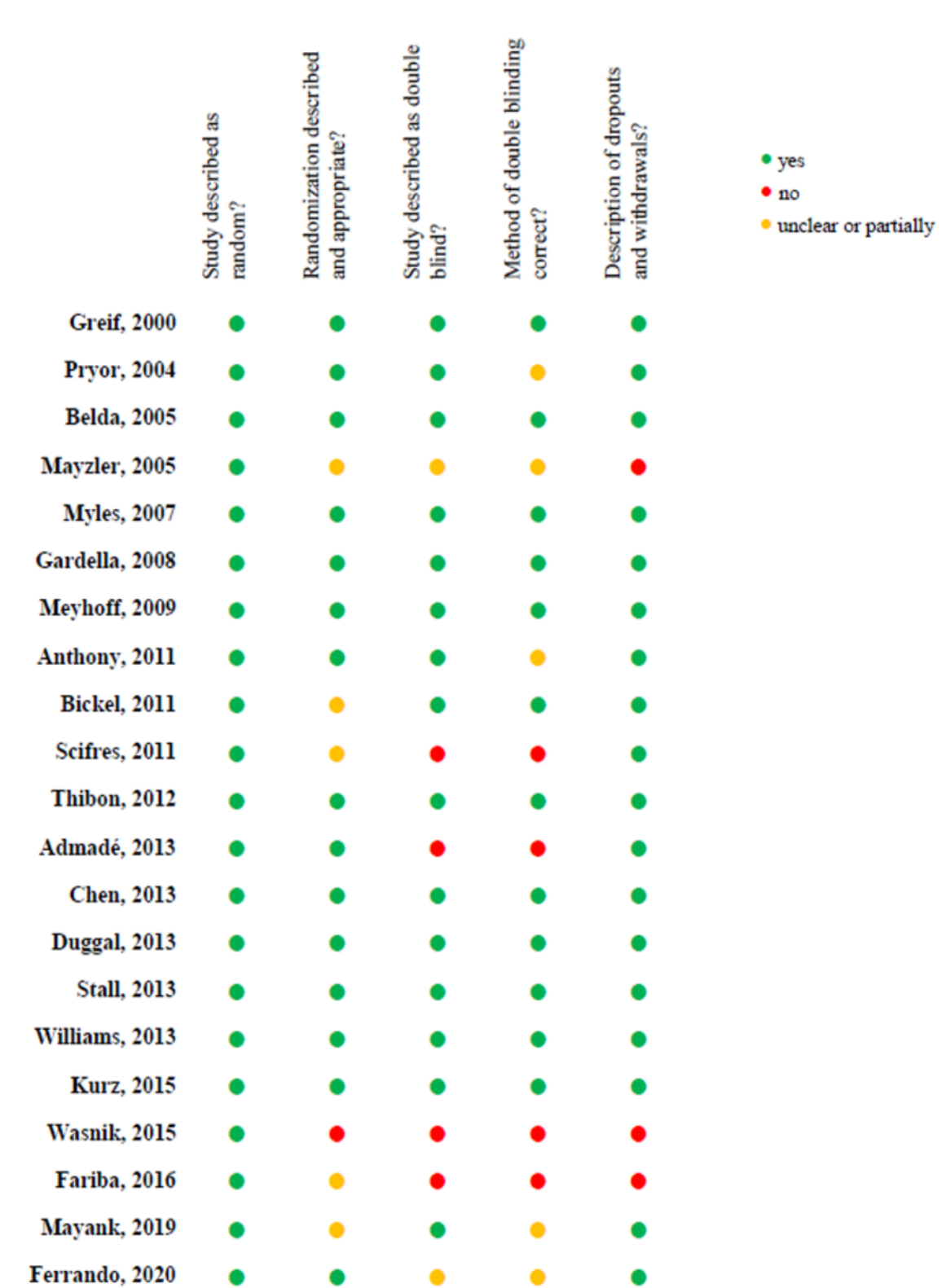

Identification
Screening
Eligibility
Included
Records identified through database searching: n = 281
PubMed = 187
Cochrane = 85
ClinicalTrials.gov = 9
Additional records identified through other sources: n = 13
Records after duplicates removing: n = 237
Records screened (titles and abstracts): n = 237
Records excluded: 195
Subject: n = 98
Type: n = 91
Population: n = 6
Full-text articles assessed for eligibility n = 42
Full-text articles excluded:
Recruiting: n = 4
Abstract only: n = 1
Intervention: n = 7
Outcome: n = 1
Retracted studies: n = 3
(+3 studies from the same group)
Studies included in the qualitative synthesis: n = 23


Study described as random?
Randomization described and appropriate?
Study described as double blind?
Method of double blinding correct?
Description of dropouts and withdrawals?
yes
no
unclear or partially
Greif, 2000
Pryor, 2004
Belda, 2005
Mayzler, 2005
Myles, 2007
Gardella, 2008
Meyhoff, 2009
Anthony, 2011
Bickel, 2011
Scifres, 2011
Thibon, 2012
Admadé, 2013
Chen, 2013
Duggal, 2013
Stall, 2013
Williams, 2013
Kurz, 2015
Wasnik, 2015
Fariba, 2016
Mayank, 2019
Ferrando, 2020