Clinical effects and adverse events of desflurane in adult patients undergoing supratentorial craniotomy: A systematic review

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Abstract

Desflurane is an inhalational anesthetic agent with an appealing recovery profile. Its use during craniotomies however, has been limited. The present systematic review investigates the clinical effects and adverse events of desflurane use during supratentorial craniotomies for brain tumor resection in adult patients, in comparison to other inhalational and/or intravenous agents. Literature search was conducted across the following databases MEDLINE, Library of Congress and LISTA (EBSCO) from January 2001 to January 2021. Twelve studies from 2003 to 2020 were included in this systematic review. Desflurane was compared to either isoflurane, sevoflurane or propofol for anesthesia maintenance. Regarding the primary outcomes studied, brain relaxation scores showed no statistically significant difference between desflurane and the other anesthetic agents. Recovery timepoints, such as time to recovery, time to eye opening, time to extubation, time to follow commands and time to reach a "Modified Aldrete Score" equal or above 9 were significantly shorter in the desflurane arm in the majority of studies. Systemic hemodynamic variables, mean arterial pressure and heart rate, as well as cerebral hemodynamics, intracranial pressure and cerebrospinal fluid pressure were comparable between anesthetic agents and desflurane, in each study. Results of this systematic review demonstrate that desflurane is a hypnotic agent with few adverse events for anesthesia maintenance in adult patients undergoing supratentorial brain tumor surgery. Large, prospective, comprehensive studies, utilizing standarized parameter evaluation could provide higher level of evidence.

Key words: anesthesia, craniotomy, desflurane, inhalational, supratentorial, volatile

Introduction

Early patient recovery after brain surgery is considered one of the main goals of the anesthesia plan. Desflurane due to its unique pharmacokinetic and pharmacodynamic profile, can contribute to prompt extubation, even after prolonged duration of anesthesia.[1] This characteristic allows early neurologic evaluation and early recognition of disastrous postoperative complications, such as seizures, increased intracranial pressure or hemorrhage can be identified and treated accordingly.

Desflurane is a fluorinated methyl ethyl ether. It has low blood/gas, fat/blood and brain/blood partition coefficients, which favor its rapid elimination and early recovery of consciousness.[2] Desflurane is advantageous due to limited metabolism and adipose tissue storage and is considered to be a safe anesthetic choice in several surgical populations.[1] Concerning cerebral physiology, desflurane can decrease cerebral metabolic rate and oxygen consumption.[3] On the other hand, regarding systemic hemodynamics, desflurane can decrease mean arterial pressure and consequently cerebral perfusion pressure. There have been doubts regarding its superiority in brain surgery, due to its physiologic effect to promote cerebral vasodilatation and increase cerebral blood flow (CBF) and cerebral blood volume both in animal and human studies.[3] In theory, this could promote an increase in intracranial pressure (ICP), which could have detrimental effects on patients with intracranial pathology. Recent studies though, have demonstrated that desflurane at 1.0 MAC does not increase intracranial pressure in normocapnic patients.[4] Over the past years, there has been an increasing body of evidence showing that desflurane can be an acceptable alternative to other volatile or intravenous hypnotic agents for brain surgery. However, to the best of the authors' knowledge, there is no systematic review or meta-analysis on this topic. Although this is not a meta-analysis, we aim to present a systematic review after examining current evidence regarding adverse and clinical effects of desflurane, as the main anesthetic agent for supratentorial brain tumor resection in adult patients.

Methods

Search strategy

A systematic search was conducted in May 2021 by two independent researchers across three databases, MEDLINE, Library of Congress and LISTA (EBSCO). Search strategy included the following terms, organized in two blocks. Block A included the terms: desflurane OR volatile an(a)esthetics OR volatile an(a)esthesia OR inhaled an(a)esthetics OR inhaled an(a)esthesia OR inhalation an(a)esthetics OR inhalational an(a)esthesia. Block B included the terms: neurosurgery OR neurosurgical OR brain surgery OR craniotomy OR intracranial OR meningioma OR glioblastoma OR supratentorial OR infratentorial. Search terms from the two blocks were combined in pairs to employ all different combinations. Literature search was restricted to articles published during the last twenty years. Reference lists of the examined articles were also searched for relevant results.

Study selection

Studies were selected according to the PICOS approach. After initial search, two reviewers independently screened the articles by title and abstract to identify pertinent studies. Articles not excluded through this process, were read thoroughly in order to determine their suitability. Exclusion criteria included non-human studies, non-adult population, case series, non-comparative studies, review articles and articles not in English. Criteria for inclusion were articles in English, prospective and retrospective comparative studies, both randomized and non-randomized, having desflurane and other anesthetic agents as comparison arms, studies on human adult population and studies on craniotomies for tumor resection. Articles that were published during the last twenty years, since 2001, were included in this review. In case of disagreement, a third independent reviewer was consulted for resolution. (See supplemental table: The PICOS model)

Data collection

Data from the included studies were extracted independently by two reviewers and cross checked by a third one. Extracted data included first author's name, year of publication, type of operation, number of patients included, demographic characteristics, anesthetic agents used, results about primary and secondary outcomes. Primary outcomes included brain relaxation score, time to emergence (minutes), time to recovery (minutes), time to extubation (minutes), time to follow commands (minutes), time to reach Modified Aldrete Score (MAS) equal or greater than 9, perioperative systemic hemodynamic parameters, mean arterial pressure (MAP) in mmHg, heart rate (HR) in beats per minute, cerebral hemodynamic parameters, intracranial pressure (ICP) in mmHg, cerebral perfusion pressure (CPP) in mmHg, lumbar cerebrospinal fluid pressure (LCSFP) in mmHg. Secondary outcomes included, perioperative gas exchange patterns (PaO_2 and $PaCO_2$ in mmHg), quality of recovery using the "Short Orientation Memory Concentration Test" (SOMCT) or "Rancho Los Amigos scale" (RLAS), perioperative blood glucose trends, emergence agitation (%), postoperative nausea and/or vomiting (PONV) (%), postoperative shivering (%), patient satisfaction (%) and survival parameters. Satisfaction about the quality of anesthesia was graded by patients on a three point scale, “dissatisfied”, “neither dissatisfied nor satisfied” and “satisfied”, twenty four hours after surgery. Regarding systemic and cerebral hemodynamics, gas exchange patterns and perioperative glucose trends, as timing of measurement differed widely across studies, only results about the presence or absence of statistical difference were extracted by the authors. Numerical results about these outcomes were not extracted and compared across studies, unless it was clear that metrics were obtained the exact same time point during the perioperative period. All information collected was tabulated to allow analysis.

Risk of bias assessment

Included studies were assessed for risk of bias independently by two reviewers. Resolution by a third reviewer was sought in case of disagreement. The Cochrane tool for assessing risk of bias in randomized trials (ROB 2) was used.[5] Methodological quality for each of these studies was assessed in five different domains and a final overall risk of bias judgement was reached. Based on the overall risk of bias judgement, studies were graded as “low risk of bias”, “some concerns” or “high risk of bias”. For non-randomized studies, methodological quality was assessed according to the “Methodological Index For Non-randomized Studies” (MINORS).[6]

Protocol

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) as CRD4202123824 on March 31, 2021. The study was conducted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7]

www.crd.york.ac.uk/prospero/display_record.php?RecordID=238243

Results

Study selection

The initial search strategy yielded forty-three studies. After deduplication and suitability screening, eleven studies were retained for analysis. Screening of reference lists yielded one additional result. Study selection is shown in figure 1. The present study finally included twelve articles published from 2003 to 2020. All included studies were prospective randomized with the exception of one retrospective study. The type of operation was supratentorial craniotomy for intracranial lesions consistently across all included studies. Although, the search strategy also included the term " infratentorial", no suitable study on infratentorial surgery was found. Therefore, the present systemic review focuses only on supratentorial craniotomy. Anesthetic agents used for comparison included sevoflurane and isoflurane, in six studies each, and propofol in two. (Table 1)

Demographics

The size of included studies varied considerably, Cata et al.[8] being the largest (261 for the desflurane arm vs 117 patients for the isoflurane arm) and Boisson et al.[9] the smallest (16 for desflurane vs 17 for isoflurane). Patients' demographics (median age in years, % female) were also considerably different across studies. Dube et al.[10] reported the youngest median age (34,9 for the desflurane group vs 39,5 years for sevoflurane), whereas Magni et al.[11] reported the oldest (60,4 for desflurane vs 62,4years for sevoflurane). Kaye et al.[12] included the highest percentage of females (66.6 in the desflurane group vs 61.1 in the isoflurane group) in contrast to Bastola et al.[13] who had the lowest (32.0 for desflurane vs 28.0 for sevoflurane vs 28.0 for propofol). (Table 1)

Primary outcomes

Brain relaxation scores was reported in five studies.[10,13,14,15,16] For the evaluation of brain relaxation, a score ranging from 1, representing completely relaxed brain, to 4, representing tight brain, was used in all studies. No study showed statistically significant difference between desflurane and other anesthetic agents. Time to eye opening, defined as the time between the anesthetic agent cessation and patient's eye opening, was reported in eight articles.[9,10,11,12,14,15,16,17] In five of them , anesthesia with desflurane resulted in significantly shorter times overall,[9,14,15,16,17] whereas the rest reported no statistically significant differences.[10,11,12] A similar trend was observed with time to extubation, which was reported in eight articles.[9,10,11,13,14,15,16,17] Statistically shorter time to extubation in the desflurane group was seen in five out of the eight studies.[9,11,14,15,17] Results concerning time to recovery were reported in seven studies,[9,10,11,14,15,16,17] although the definitions implemented for recovery were inconsistent across them. For this review, "time to recovery" was defined as the time from anesthetic agent's discontinuation to patient's orientation after verbal stimuli. Statistically significant results reporting shorter times with desflurane were seen in five studies,[9,11,15,16,17] whereas the other two studies reported no statistical difference.[10,14] Similarly with time to recovery, a clear and common definition of the time to follow commands was not available across the included studies. Three studies reported results about time to follow commands[12,13,16] and two reported about time to hand gripping.[9,17] In the present review, time to hand gripping was considered the same as time to follow commands. In four out of five studies, anesthesia with desflurane resulted in shorter time with statistically significant difference .[9,13,16,17] Time to reach a score equal to or greater than 9 according to MAS was reported in three studies,[14,17,18] all reporting significantly shorter times in the desflurane arm. One study used a MAS equal to or above 8 in their methodology,[15] also reporting significantly shorter time with desflurane.

Regarding systemic hemodynamics, results about MAP and HR were reported in seven[4,9,10,12,13,14,15] and eight studies, [4,9,10,12,13,14,15,16] respectively. Mean arterial pressure values were reported to be comparable in the majority of the studies. However, one study[15] showed significantly higher MAP values with desflurane at various timepoints (Table 2). Heart rate values between desflurane and other hypnotic agents were, also, comparable in all studies except one, which reported statistically higher values in the sevoflurane arm.[13] Intracranial pressure, CPP and LCSFP were measured and reported in four,[4,10,12,16] two[4,12] and one[12] studies, respectively. No study reported statistically significant difference. Results about primary outcomes are shown in Table 2.

Secondary outcomes

Despite the fact that results about these parameters were scarcely reported, authors considered them important for the scope of this review. Evaluation of recovery after anaesthesia using SOMCT was completed in three out of the twelve studies.[14,10,11] In two studies,[11,14] the desflurane group had significantly higher SOMCT scores, indicating improved recovery, but only at earlier time points (Table 3). No difference was shown at later timepoints. RLAS results were reported in one study and results showed a similar trend as with SOMCT.[14] Gas exchange pattern trends, namely, PaO_2 and $PaCO_2$, were studied in three[11,14,16] and four articles,[4,11,14,16] respectively. The majority of the articles did not show a statistically significant difference. Only one study demonstrated statistically lower $PaCO_2$ values in the desflurane arm at two timepoints, 15 and 30 min post extubation.[14] Perioperative blood glucose trends, among anesthesia with desflurane, sevoflurane and propofol were reported in, only, one study that showed statistically significant results in favor of propofol for achieving steadier blood glucose levels.[18] Emergence agitation was reported in two studies.[10,13] Neither of the results was statistically significant. The incidence of postoperative nausea and/or vomiting (PONV) and postoperative shivering was reported in seven[9,10,11,13,14,17,18] and four studies,[9,10,11,14] respectively. None of these studies showed a statistically significant difference. Patient satisfaction after anesthesia was reported in one study.[18] There was no difference in rates of patient satisfaction among those who received desflurane, sevoflurane, or propofol. Only one retrospective study measured long-term survival after craniotomies for glioblastoma multiforme.[8] Desflurane and isoflurane were found to have comparable progression free survival (PFS) and overall survival (OS) rates. Overall survival rates at three years were found to be 0.27 in the desflurane group and 0.35 in isoflurane arm, whereas, at five years the desflurane arm had a survival rate of 0.15 compared to 0.16 with isoflurane. Secondary outcomes results are shown in Table 3.

Risk of Bias (Rob2)

No disagreements between the reviewers were encountered while assessing for risk of bias. Two studies were assessed as having an overall high risk of bias.[9,10] The first was due to having some concerns regarding “deviations from intended interventions” and due to having high risk in “measurement of the outcome”. [9] The second was due to raising “some concerns” in three domains “randomization process”, “deviations from intended interventions” and “measurement of the outcome”. [10] Three studies had a moderate overall risk of bias.[11,13,17] The studies of Gökçek et al.[17] and Bastola et al.[13] raised “some concerns” in two categories: “deviations from intended interventions” as well as “measurement of the outcome”. Study of Magni et al.[11] raised “some concerns” in “randomization process” and “deviations from intended interventions”. Six studies were appraised as having a low risk of bias in each domain and overall.[4,12,14,15,16,18] A summary of Rob2 assessment is depicted in Figure 2.

MINORS criteria

One retrospective non-randomized study was assessed using the MINORS criteria.[8] For comparison purposes, scores were calculated for all the studies. The scores ranged between 10[9,13] and 14[14,17,18]. The one non-randomized retrospective study was assigned a score of 13. [8] Overall, the main reasons for missing points were, “follow-up duration” declaration and “loss to follow-up” declaration. Among all studies only Cata et al.[8] presented accurate data on both categories. Failure of a clear statement regarding “inclusion of consecutive patients” was the second most common reason for missed points. Four studies received the maximum of 2 points, [12,14,17,18] six studies received the intermediate of 1 point,[8,10,11,13,15,16] and two studies received no points.[4,9] Outcome evaluation bias was the third most common reason for missing points. Six studies received a maximum score,[11,14,15,16,17,18] one study received no points,[8] and five received 1 point.[4,9,10,12,13] Evaluation according to the MINORS criteria is summarized in supplemental digital content table: MINORs scores.

<u>**Discussion**</u>

With reference to primary outcomes studied in this review, desflurane proves to be an anesthetic with few adverse events in craniotomies for brain tumor resection in adult patients. Systemic and cerebral hemodynamic variables, as well as brain relaxation scores were comparable between desflurane and other anesthetic agents with no statistically significant difference. Moreover, anesthesia maintenance with desflurane consistently resulted in shorter recovery times. It should be noted, though, that all patients included in this review showed normal ICP values preoperatively. Regarding secondary outcomes, quality of recovery after anesthesia using SOMCT and RLAS test appeared to be better with desflurane, but statistically significant only at the earlier postoperative period. In a similar trend, $PaCO_2$ did not differ in most of the studies, except for one study[14] in obese patients, which reported statistically lower $PaCO_2$ values in the desflurane arm, but only at earlier time points of the first postoperative hour. Clinically, this translates to lower postoperative sedation in the desflurane group. Emergence agitation, POVN, postoperative shivering and patient satisfaction were all statistically comparable among the anesthetic agents. Finally, statistically significant results against desflurane were reported only by Haldar et al. regarding perioperative blood glucose values.[18] In this study, the propofol group achieved more stable plasma glucose values perioperatively compared to desflurane and sevoflurane.

To the best of the authors' knowledge, this is the first systematic review on this topic. A recent narrative review,[19] showed findings similar to ours and supports the role of third generation fluorinated hypnotic agents in adult patients undergoing craniotomies. Regarding recovery parameters in other surgical populations, a number of systematic reviews and meta-analyses are available. In the case of elderly patients, Chen et al. concluded that desflurane arm had consistently statistically significant shorter recovery times compared to sevoflurane.[20] Also, in a meta-analysis by Singh et al. comparing recovery profiles in bariatric surgery similar results are reported, in favor of desflurane.[21]

Regarding ambulatory surgery this time, a systematic review by Gupta et al. and a meta-analysis by Chen et al. concluded with agreeing results to the above.[22,23] It appears that desflurane's pharmacological properties make it a very appealing anesthetic agent, for a broad range of surgical populations, from shorter ambulatory surgery to longer lasting craniotomies, where rapid recovery is necessary for a complete and precise neurological assessment. A study by Ghoneim et al. not included in this review, due to reference to pediatric population, reported no difference in brain swelling with desflurane, isoflurane and sevoflurane and showed significantly faster recovery times in the desflurane group.[24]

All studies were assessed on the basis of their primary outcomes, for which a power analysis was performed. The most frequent problems encountered were with respect to "randomization process", "deviations from intended interventions" and "measurement of outcome". In the study by Magni et al.[11] the groups could not be considered equal due to a small but statistically significant difference in the MAC-hours, a parameter that directly influences the primary outcome (time to emergence/extubation). In this case, we have to consider the possibility that desflurane's rapid recovery is due to shorter exposure to the agent instead of its pharmacokinetic properties. We suggest that in the future more studies state the MAC-hours, as it is a more objective way to assess the equality of the groups, compared to anesthesia or surgery duration. The study by Dube et al.[10] was marked as raising "some concerns" because although baseline differences among the groups were not significant, the specific process of randomization was not described. In the category of deviations from intended interventions, five studies presented a moderate risk of bias, as they were not double-blinded.[9,10,11,13,17] Gokcek et al.[17] mentioned that the data-collector was blinded to the agent but the anesthesiologist in charge of interventions was not, and the concentrations of the volatile anesthetics were not constant during the study.

For the remaining studies, [9,10,11,13] the main problem was that the anesthesiologist in charge of extubation and assessment of recovery time was not blinded to the agent. With respect to “measurement of the outcome” the main reasons for reporting moderate or high risk of bias were unmeasured differences between groups concerning total doses of other anesthetics (e.g. opioids), vague criteria concerning important time points (extubation criteria, eye opening/ spontaneous ventilation upon stimulation or not), concomitant use of N_2O and tapering of volatile agents in a possibly not uniform way among the groups.

The main reason for missed points according to MINORs assessment was loss of follow-up or issues with follow-up duration. None of the studies except for one[18] dealt with long-term oncological outcomes such as tumor recurrence and survival parameters. These are matters of particular importance, since the study population concerned oncology patients. Another reason for low MINORS scores, was failure to include consecutive patients, although reasons were stated on most occasions. Outcome evaluation bias was judged based on blinding. Only one study received zero points due to the retrospective nature of the study. [8] All other studies received a score of 1 (inadequate blinding) or 2 (adequate blinding- blind evaluation of objective endpoints and double-blinded evaluation of objective endpoints).

The present study was a systematic review of a relatively small number of relevant articles, and as such, publication bias cannot be excluded. Moreover, although most of the papers included derived from randomized comparative studies, the authors of the present review decided not to attempt a numerical aggregation in the form of a meta-analysis. The main reason was the heterogeneity in the definition of certain time-related parameters. Also, one of the included studies that received a high score according to the MINORS criteria, had some issues according to the ROB2 assessment.[17] This leaves two articles with high scores according to both assessments.[14,18] Haldar et al.[18] however, did not report several parameters, that the authors of the present review considered clinically pertinent. It is also worth mentioning that possible important outcomes which indicate patients' functional status ,such as Glasgow Coma Scale, Modified Rankin score or postoperative stroke are scarce or non-existent across current literature. Short orientation memory concentration test and Rancho Los Amigos score, which test neurological functional ability, only appear in three and one article each, respectively. Overall, this study attempted in the most structured and objective way to sum up relevant evidence on the topic, however its shortcomings reflect the limitations in current literature.

It becomes evident from the above comments that the most important limitation of current literature is the heterogeneity in the reporting of certain endpoints. Thus, a consensus needs to be reached regarding the best way to assess time-related parameters. In addition, blood glucose levels throughout the procedure, hemodynamic, oncological and patient satisfaction endpoints are very important and need to be reported consistently in future studies. An adequate number of further good quality and homogenous randomized studies are required for a meta-analysis to provide the most reliable answers to the clinical questions this study has examined.

Conclusion

Overall, in the present systematic review no study was found where the rate of adverse events was statistically significantly worse in the desflurane group compared to other anesthetic agents, in adult patients undergoing supratentorial brain tumor surgery. Systemic and cerebral hemodynamics as well as brain relaxation scores showed no difference between desflurane and other anesthetic agents, within each study. Concerning recovery parameters, anesthesia maintenance with desflurane consistently produced superior results. Large, prospective, comprehensive studies, utilizing standardized parameter evaluation could provide a higher level of evidence.

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Figure legends:

Fig 1: PRISMA flow diagram

Fig 2: Risk of bias assessment: Rob 2 scores

Supplemental digital Content 1: SDC table.docx, The PICOS model

Supplemental digital Content 2: MINORs scores.docx, MINORS scores