EVALUATION OF SAFETY OF USING SEDATIVE ANESTHESIA IN PEDIATRIC DENTAL CARE: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Due to its well-known benefits, propofol is one of the most commonly used medications for paediatric sedation; yet, significant concerns exist regarding respiratory and/or cardiac problems in propofol-treated kids. Propofol is being used off-label for this use in many countries, despite the fact that numerous studies have been done to compare it to other sedative drugs or opioids for children undergoing various procedures.

Materials and methods: In order to offer a comprehensive summary of the data that might be taken into account we conducted a systematic review and meta-analysis of those studies. All the studies conducted before 2019 were included from the online sources like "MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials".

Results: The included thirty studies revealed that propofol sedation was superior to other medications in terms of recovery time without raising too many concerns about adverse cardiovascular or respiratory events. Its safety profile in terms of delirium, vomiting, or nausea was comparable to that of other medications.

Conclusion: The evidence as a whole indicates that regulatory decisions regarding propofol sedation for paediatric procedures should be viewed more favorably.

Key words: Propofol, Paediatric, Sedation, Systemic Review, Anesthesia.

INTRODUCTION

A sedative-hypnotic taken intravenously, propofol has benefits such as a quick onset and offset, nausea, and the emergence of delirium 1-3. Due to its well-known benefits, propofol is frequently used to calm children who are anxious or need to be sedated during therapeutic or diagnostic procedures including "cardiac catheterization, endotracheal intubation, urgent orthopaedic, dental, or radiological imaging". Propofol is also known to have a potent sedative effect on children that might be classified as deep sedation or general anesthesia4. Propofol sedation may therefore have a slightly higher risk of resulting in respiratory or cardiovascular adverse effects than other sedative medicines. Since 2000, many studies in diverse settings were done to compare the efficacy and safety of propofol with those of other alternative sedatives5-8. Propofol has been authorized for paediatric use in GA for some age groups in some countries, including the European Union1 and US9-11; however, it is still being used off-label for paediatric procedural sedation in many nations.

A systematic review and meta-analysis of randomised controlled clinical trials (RCTs) comparing propofol with other sedative drugs or opioids for children undergoing various procedures was conducted in the current study to provide an overall summary of the evidence that may be taken into account for future regulatory decisions, including reimbursement policies.

METHODOLOGY

Searching for the articles: All the studies conducted before 2019 were included from the online sources like "MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials". "Infant, child, adolescent, propofol, sedation, and randomised controlled trial" were the main search terms utilised.

Selection standards: Studies included children <19 years, compare "propofol or propofol combination regimens with other sedative drugs or opioids" for procedural sedation, provide data from safety evaluations, and use a parallel RCT design in order to be eligible. Only English-language papers were searched. Only pertinent studies were taken into consideration when reading letters to the editor, abstracts, and meeting proceedings.

Extraction Of Data: Each article's "first author's name, publication year, participant age, number of randomly assigned patients, procedure type, provider type, American Society of Anesthesiologists class, information on the intervention and control treatments, recovery time, haemodynamic responses, and adverse events" were all taken out. According to the adverse event reporting tool the adverse events were categorised as "minor, moderate, or major" depending on their severity or clinical value. The minimum values of the "hemodynamic responses (HR, MBP)" were derived after repeated measurements of the hemodynamic responses during drug infusion. When trials included multiple treatment arms, the meta-analysis included each pairwise comparison with a "shared" group, and the "shared" group was distributed equally among the comparisons.

Evaluation of the listed studies' bias risk: The risk of bias in each of the following areas: "completeness of data, selective result reporting, sufficiency of sequence generation, adequacy of allocation concealment, adequacy of blinding, and other potential threats to validity" were assessed. When there was insufficient information supplied to allow for a judgment, the first four domains were classified as "acceptable" for low risk, "inadequate" for high risk, and "unclear" for unknown risk. The trial was classified as having a risk of selective outcome reporting whenever evidence of selective disclosure or the suppression of pre-specified outcomes was discovered. Studies that used preliminary analysis or had a sample size of fewer than 25 kids were given further consideration since they might have additional potential challenges to validity.

Statistical Investigation: For continuous and dichotomous data, the WMD and the RD were derived, respectively. When the pooling was deemed plausible and there was minimal statistical heterogeneity, a "random-effects model" was used to construct pooled effect estimates with 95 percent confidence intervals and test for differences in effects at the 5% significance level. I2 statistics were used to measure heterogeneity, with I2 values below 75% being deemed to indicate high and significant heterogeneity45. Where possible, a subgroup analysis was conducted to investigate study heterogeneity. An effort to qualitatively explain the potential origins for the varied outcomes when it was not feasible to undertake a formal analysis was made. The type of procedures carried out, the medications used as controls, the type of provider, the treatment plan, the definition of outcomes, and research quality were among criteria that were taken into consideration as potential explanations for heterogeneity.

An "upgraded funnel plot" with contours and the "Egger test" were used to assess the presence of publication bias and small study effects. The "trim and fill method" was used to create estimates of the meta-analysis taking the potential bias into account as a sensitivity analysis when evidence of small study effects was found. We selected all moderate and significant adverse effects that were documented in enough research for these investigations.

For all analyses, STATA version 12 ("Stata Corp., College Station, TX, USA") was used.

RESULTS

Investigate characteristics: Thirty studies met the inclusion criteria12-41. Orthopaedic procedures (4 studies), intubation (2 studies), gastrointestinal procedures (4 studies), dental procedures (4 studies), cardiology procedures (6 studies), magnetic resonance imaging (MRI) (6 studies), and other procedures were performed in the included studies (4 studies). Propofol was used alone in most MRI studies, but it was also frequently combined with "ketamine, midazolam, or opioids for other procedures. Dexmedetomidine, ketamine, or midazolam" were most frequently compared to propofol sedation as a single agent, in combination, or in combination with other drugs such as opioids. "Anaesthesiologists (10 studies), sedating physicians or nurses (2 studies), physicians (4 studies), and intensivists (1 study)" were the providers in charge of administering sedation, but other studies did not specify the providers.

Bias: Twelve of the thirty studies (40%) used appropriate randomization methods, such as computer random number generation. Three studies were deemed insufficient because "coin flipping25, allocation by enrolment day39, or admission day19" were used. Eleven studies (37%), such as central allocation or sealed envelopes, reported adequate allocation concealment methods. Two studies19,39 that used a quasi-randomisation method were deemed insufficient for allocation concealment. Twelve studies (40%) reported blinding or only used objective outcomes. Seven studies did not use blinding methods or used subjective outcomes without blinding.

Twenty-five studies (83%) used the intention-to-treat approach or had dropout rates of less than 5%. Three studies had questions about the completeness of their data. Some results for outcomes mentioned in the methods

section were missing in 8 studies so we determined that a risk of selective reporting bias was present. Five studies with results from a small preliminary study and/or a sample size of fewer than 25 children were considered to be at risk of bias from other sources.

Recovery time: Nineteen studies with 20 comparisons provided data on recovery time (**Fig. 1**), with 10 evaluating propofol as a sole agent and the others using it in combination with other sedatives or opioids. Although the definitions of recovery time varied slightly across studies, it could be roughly defined as the time interval between the completion of the procedure and the achievement of discharge criteria. When propofol was used alone, the pattern of relative time reduction was consistent and clear. Although statistical heterogeneity remained high within this subgroup, this was due to the magnitude of the effect rather than its direction. When propofol was combined with opioids or when propofol and the control sedative were combined with the same concomitant drug, the magnitude of the effect became more variable, but with a clear tendency to decrease in time. However, when propofol in combination with another sedative was compared to another sole sedative, the results revealed a different pattern. As a result, no overall pooled effect size was calculated.

Haemodynamic responses: Although significant statistical heterogeneity was observed, there was an overall tendency for heart rate (HR) to increase and mean blood pressure (MBP) to decrease in response to propofol use alone or in combination with another sedative or opioid.

Minor adverse events: Coughing was reported in two RCTs. Coughing was observed in 7 of 10 children in the propofol group, but not in any of the 20 children in the midazolam or ketamine groups. However, there was no statistically significant difference between patients who received propofol in combination with an opioid and those who received other sedative combinations. Due to heterogeneity, these results were not combined.

In 10 RCTs with 12 comparisons, there was no significant difference in the incidence of nausea or vomiting between propofol regimens and comparator groups. In some studies33,37, propofol was associated with a significant reduction in the incidence of nausea or vomiting, but these findings were not clearly defined. One study12 had a significantly higher rate of nausea and vomiting than other studies, but this did not result in statistically significant treatment difference heterogeneity. Nine studies examined the occurrence of emergence agitation at various time points. Overall, the use of propofol resulted in a marginally significant risk reduction.

Adverse events of moderate severity: Eighteen studies with 19 comparisons reported cardiovascular issues. In 15 studies, the risk of hypotension did not differ between propofol-based regimens and other sedative or opioid groups. Bradycardia and tachycardia differed only marginally.

Data on respiratory complications were provided by 22 studies with 27 comparisons, and there was an overall trend toward an increased risk of respiratory adverse events when propofol was used. However, in terms of the incidence of a decreased respiratory rate, the trend of increasing risk was not statistically significant. Although there was a significant difference in the incidence of oxygen desaturation between the propofol and comparator groups, the RD and 95 percent CI were small due to an exaggerated observation in a small study35. Only two studies with five comparisons reported the occurrence of hypercapnia. In one study38, patients who only received propofol had a higher incidence of hypercapnia than the other four comparison groups.

Significant negative events: Both laryngospasm and apnoea occurred infrequently, regardless of whether propofol was administered (**Figs 2 and 3**). As a result, no significant RD was observed for those events comparing propofol regimens to comparator groups. Even when this result was included, the resulting RD was still small19. Airway support was also rarely required in many studies, whether propofol was used or not, with no RD between groups (**Fig. 4**). One study also reported the need for airway support, but we did not include those results in the meta-analysis because their dramatically different scale of incidence was not actually related to the sedation regimen; the event was more broadly defined in the study36.

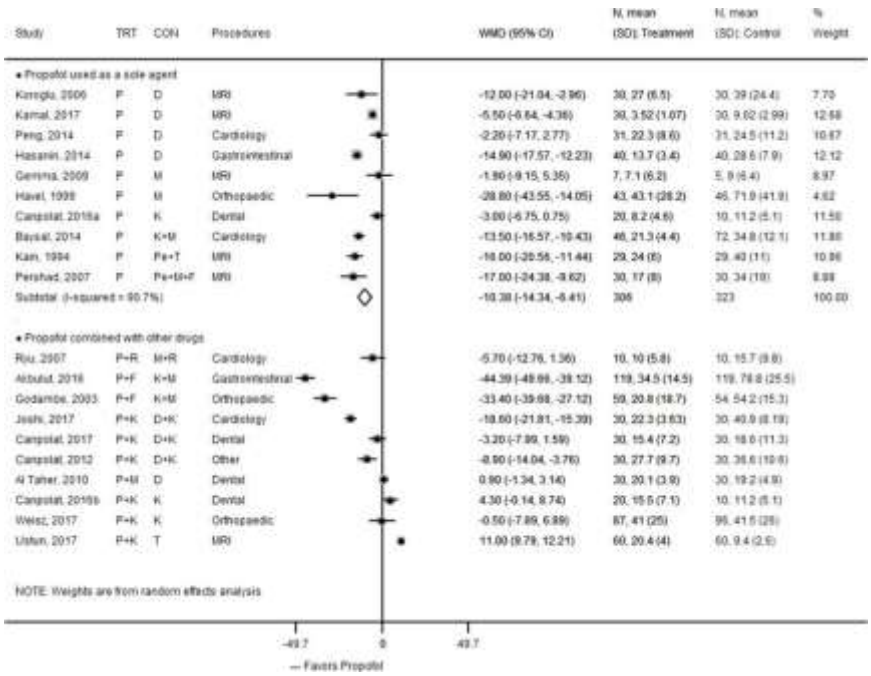

Figure 1. Forest plot for recovery time. "Abbreviations: CI, confidence interval; CON, control; D, dexmedetomidine; F, fentanyl; K, ketamine; M, midazolam; MRI, magnetic resonance imaging; P, propofol; Pe, pentobarbital; R, remifentanil; SD, standard deviation; T, thiopental; TRT, treatment; WMD, weighted mean difference (in minutes)."

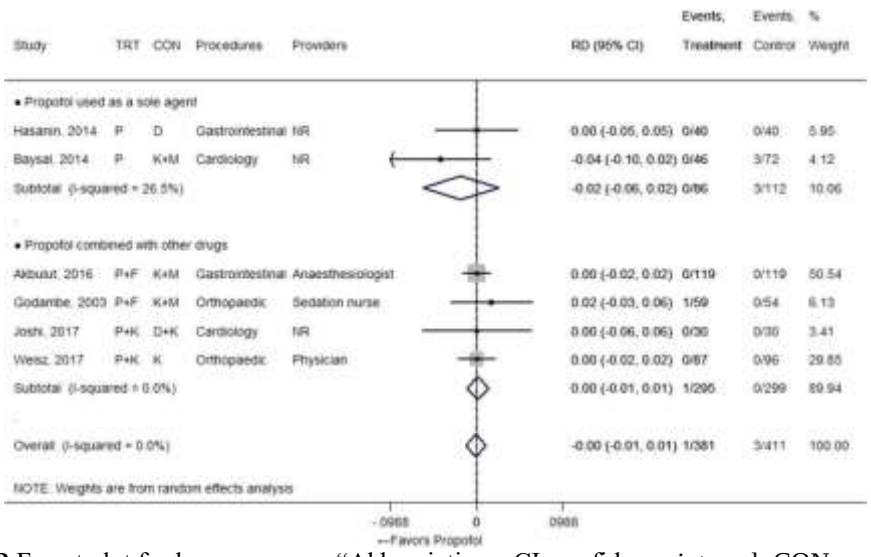

Figure 2. Forest plot for laryngospasm. "Abbreviations: CI, confidence interval; CON, control; D, dexmedetomidine; F, fentanyl; K, ketamine; M, midazolam; NR, not reported; P, propofol; RD, risk difference; TRT, treatment."

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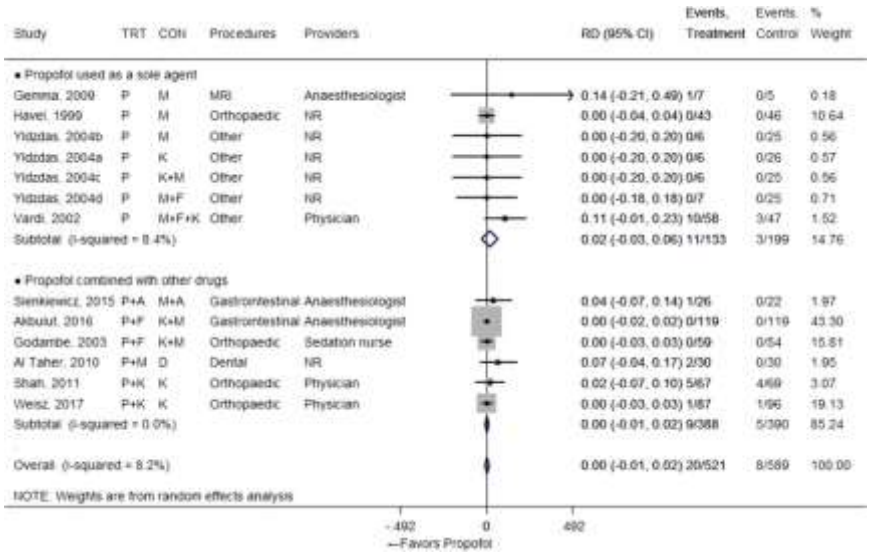

Figure 3. Forest plot for apnoea. "Abbreviations: A, alfentanil; CI, confidence interval; CON, control; D, dexmedetomidine; F, fentanyl; K, ketamine; M, midazolam; MRI, magnetic resonance imaging; NR, not reported; P, propofol; RD, risk difference; TRT, treatment."

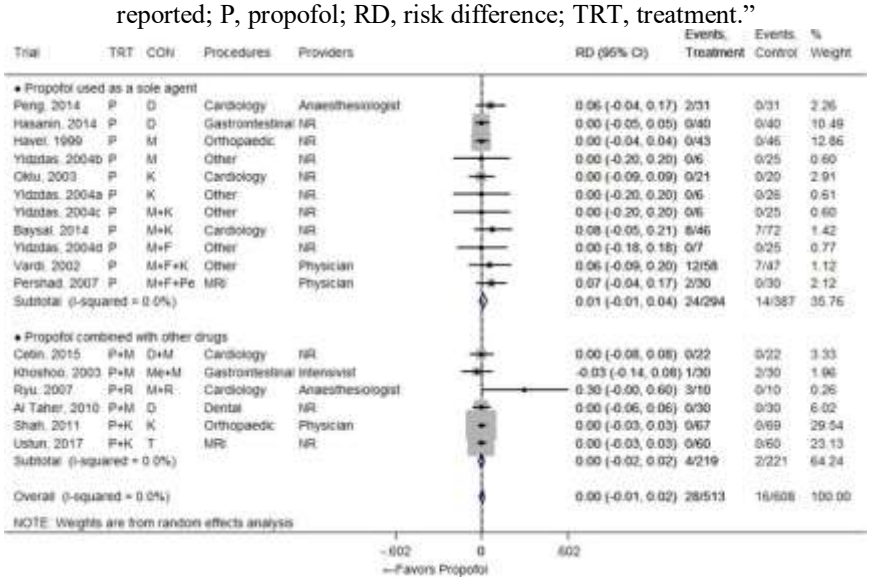

Figure 4. Forest plot for need for airway support. "Abbreviations: CI, confidence interval; CON, control; D, dexmedetomidine; F, fentanyl; K, ketamine; M, midazolam; MRI, magnetic resonance imaging; Me, Meperidine; Mt, methohexital; NR, not reported; P, propofol; Pe, pentobarbital; R, remifentanil; RD, risk difference; T, Thiopental; TRT, treatment."

DISCUSSION

The goal of this study was to assess the overall safety of using propofol for procedural sedation in paediatric patients in a variety of clinical settings. Because sedation is a continuum, and children can easily slip into a deeper level4, the terminology for propofol sedation or anaesthesia is often confusing. However, depending on whether an invasive airway device, such as a "laryngeal mask airway or endotracheal tube", is required, a distinction between planned sedation and planned GA is made42. As a result, when the use of an invasive airway device was planned, the intended level of sedation was classified as GA.

Our meta-analysis included 30 studies that included 3,774 children who were given propofol, other sedatives, or opioids for a variety of procedures. We discovered that a variety of treatment strategies were used for paediatric sedation during non-painful or distressing procedures. Most studies used propofol alone for non-painful procedures. Many studies used propofol in combination with opioids for painful procedures. The treatment regimens of the control drugs, on the other hand, were far more varied. Although the dose of propofol in the combination regimen would be lower than in the propofol-only sedation regimen, we discovered that the incidence of some dose-dependent side effects, such as hypotension and decreased respiratory rate, was generally similar across studies. Some small studies found that the rates of hypotension, reduced respiratory rate, desaturation, and apnea were higher, resulting in asymmetric skewed funnel plots. A trim and fill analysis revealed that the use of propofol sedation had no significant associations with the occurrence of respiratory and

cardiovascular adverse events.

A previous large multi-institutional observational study with no controls looked into adverse events during propofol sedation in children for procedures4. The "Paediatric Sedation Research Consortium" conducted this study, which suggested that propofol sedation is unlikely to have serious adverse outcomes, such as mortality and cardiac arrest, and the authors also noted that such results rely on institutions' ability to manage less serious events, such as "laryngospasm, airway obstruction, and apnea".

This study focused on potentially serious or moderate adverse events associated with propofol in comparison to other sedative or opioid drugs, and our findings suggest that the incidence of those adverse events in propofol regimen groups, using propofol either as a sole agent or in combination with other sedatives or opioids, was comparable to the incidence in control groups. The previous study found that patients' "American Society of Anesthesiologists" status and age group were significantly associated with adverse events, but such an investigation was not possible in our study due to the nature of the analysis, which was based on aggregated data extracted from published studies. Although we attempted to provide information on the type of provider alongside the analysis results in order to investigate the impact of this factor on the safety results, no formal analysis could be performed because relevant information was not available in approximately 43 percent of the studies included in the analysis. However, no significant trend associated with these factors was observed based on the descriptive information that we extracted and presented alongside the results of safety outcomes.

The limitations included that since the studies were trials the expertise used in them might be different than the routine clinical proceedings. Different studies used different doses based on the clinical pertinence. There were studies with high risk of bias.

CONCLUSION

Finally, when compared to other drugs, propofol sedation improved recovery time without raising concerns about cardiovascular or respiratory adverse events. It had a similar safety profile to other drugs in terms of coughing, nausea or vomiting, and emergence delirium. Taken together, the evidence suggests that propofol could be considered for sedation for paediatric procedures as a viable alternative to other options. Propofol sedation should be considered for regulatory approval for paediatric procedures.

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