Intra Operative Use of Anti Emetic Drugs for Children Undergoing Full Dental Rehabilitation under General Anesthesia. A Double Blind Randomized Clinical Trial

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Background: *Postoperative Nausea and Vomiting (PONV) is a common complication following dental treatment under general anesthesia (DGA) that may lead to unplanned hospitalization, increased costs and dissatisfaction of parents.* ***Aim:*** *To investigate the incidence of Postoperative Vomiting (POV) on children who underwent dental rehabilitation under general anesthesia and to compare possible preventive effect of Dexamethasone and Ondansetron on occurrences of POV.* ***Study design:*** *A double blind randomized parallel clinical trial was carried out on 352 ASA I children who underwent DGA in a private Saudi hospital in Jeddah. Children were allocated randomly to four groups. Group D of 91 children, received Dexamethasone PONV prophylaxis, group O of 87 children received Ondansetron, group DO of 93 children received combination of the two drugs and group C the control group of 81 children. The three groups were investigated by blinded dental staff for POV episodes, number of times analgesia was needed and post anesthesia care unit time (PACUT).* ***Results:*** *There was a no significant difference between the two drugs on POV. There was a significant difference in POV between control group and groups D, O, and DO. There was significant reduction in need for analgesia in the Dexamethasone groups. The three groups, which had PONV prophylaxis, showed significant reduction in PACUT compared to control group.* ***Conclusions:*** *Antiemetic drugs are useful adjuncts in DGA. Some dental procedures may have higher emetic potential than others. The type of dental procedures done is to be considered when deciding the drug profile in children undergoing DGA.*

INTRODUCTION

Postoperative Nausea and Vomiting (PONV) is a common complication of anesthesia and a major distressing complaint from pediatric patients and their parents[1]. This complication may have an adverse effect on the overall parental satisfaction and might as well cause delay in patient discharge or unexpected hospitalization with subsequent unexpected raise in the costs of dental treatment under general anesthesia (DGA)[2, 3].

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It is often difficult to determine the actual occurrence of PONV in children because nausea as a subjective symptom may remain undetected, therefore, children are thought to develop more PONV than adults with a rate ranging from 8.9% to 42%[4]. In 2000, Kovac[5] reported multiple factors to be involved in the etiology of PONV; among these is the type of surgery performed. In surgeries such as strabismus, tonsillectomies and hernia repair the incidence of PONV could exceed 50%[6]. Till now, little research work was carried out on the incidence of PONV following dental procedures under general anesthesia. The most common antiemetic drugs available for the prophylactic treatment of PONV are the serotonin 5-HT_3 receptor antagonist (Ondansetron) and Dexamethasone whose mechanism of action is still unknown[7].

The aim of this work was therefore, to investigate the incidence of Postoperative Vomiting (POV) on children who underwent full dental rehabilitation under general anesthesia and to compare the possible preventive effect of Dexamethasone and Ondansetron on the occurrences of this complication. This was tested in a controlled randomized observer-blinded study in children subjected to dental procedures under general anesthesia. The outcome measures were the incidence of POV and recovery parameters.

MATERIALS AND METHOD

A double blind randomized parallel clinical trial was done on children that underwent full dental rehabilitation under general anesthesia in a Joint Commission for International Accreditation (JCIA) accredited private hospital in Jeddah Saudi Arabia during 2011 (Figure 1).

Institution ethical approval of concerned committees based on the hospital's Corporate Social Responsibility (CSR) standards was obtained. Informed consents were obtained from parents or guardians following JCIA standards and complying with the World Medical Association Declaration of Helsinki on ethical principles for medical research involving human subjects, October 2001[8].

Inclusion criteria

Children selected for the study were healthy ASA I who underwent DGA for lack of cooperation to establish satisfactory restorative work or due to the substantial amount of dental treatment needed.

Exclusion criteria

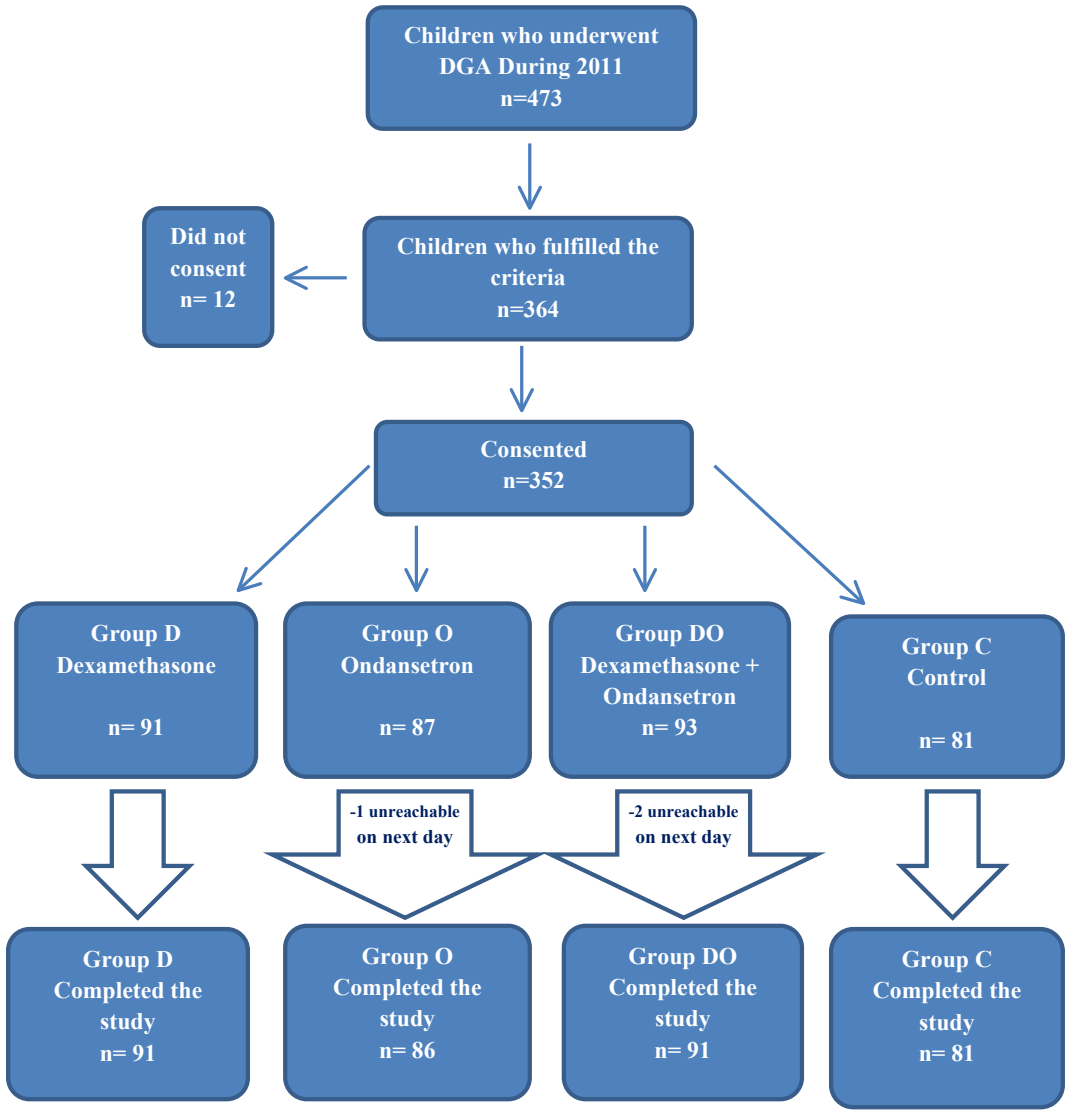
Children excluded from the study were those who had history of PONV and those who needed DGA exclusively for non-restorative procedures e.g. oral surgery, suturing cut wounds, orthodontic surgery, fractures and surgical removal of supernumerary teeth.

Three hundred and fifty two children have fulfilled the criteria for inclusion. The children were allocated to three groups. group D of 91 children who received intravenous Dexamethasone in a dose of 200 µ/Kg (maximum dose of 8 mg), group O of 87 children who received Ondansetron 100 µ/kg (maximum dose of 4 mg), group DO of 93 children who received both doses of Dexamethasone with Ondansetron and group C the control group of 81 children who did not receive antiemetic drugs.

Randomization, Standardization and Sample Size

A child undergoing DGA was to be interviewed one or two days prior to the operation day for preoperative anesthesia assessment by the anesthetist. During these interviews, the anesthetist randomly

Figure 1 Flow chart of children included in the study



allocated the children to one of the four groups on 1:1:1:1 basis. With the aid of a biostatistician some alterations were made to ensure that the four groups have no statistically significant demographic differences. The long waiting list allowed for these adjustments to be done and resulted in differences in the number of children allocated of each group.

The incidence of POV in the targeted population was found to be around 30%[9]. Using a type I error of 0.05 and a type II error of 0.2, the current trial needed 400 patients to detect a clinically important reduction in the primary outcome of POV from 30% to 10%. Based on this calculation, the number of children recruited in the current study exceeded 400 children for possible drop out and withdrawals.

Same anesthesia protocol was carried out for all four groups. Children were not allowed to eat or drink for at least 6 hours before the procedure. Thirty minutes prior to induction, the child was premedicated with oral midazolam (Dormicum®, Roche, Brussels, Belgium, 0.4 mg/kg maximum total dose was 20 mg). Induction was carried out via a facemask with 8 % Sevoflurane Abbott Co. in 100 % oxygen. After loss of consciousness, an intravenous line was established through which maintenance iv fluids are infused and bolus Propofol 2mg/kg, (Diprivan® AstraZeneca Co.) was administered to allow nasotracheal intubation. Anesthesia was maintained with Sevoflurane® around 2 % in a mixture of oxygen and nitrous oxide at FiO2 0.4. All children were nasally intubated to allow for freedom for the pediatric dentist to check occlusion. Lungs were ventilated with SIMV mode with tidal volume 8mL/kg and respiratory rate appropriate age to maintain normocapnia. An oropharyngeal pack was inserted to prevent aspiration of water and dental material fragments into the patient's airway. Intraligamental local anesthesia was administered prior to extractions and steel crown insertions while intrapulpal route was used for pulpotomies in order to help control physiologic pain reaction during the procedure[10]. At the end of surgery the trachea was extubated and the child was nursed in the lateral post-tonsillectomy position.

For study purpose, a standardized definition of vomiting was adopted from Maule, 1990[11] that is the forceful expulsion of liquid or solid gastric contents. Accordingly, retching (the simultaneous contraction of the abdominal muscles and muscles of inspiration that may occur with vomiting) was not counted as vomiting.

To investigate possible effect of both drugs (Dexamethasone and Ondansetron) on postoperative need for analgesia, each group was divided into two sub-groups. According to the number of Painful Dental Procedures (PDP), each group was divided into a less than three PDP's subgroup and 3 or more PDP's subgroup.

Dental extractions as well as inserting preformed metal crowns (PMCs) were considered as treatments which provoke post-operative pain [12,13]. Given the fact that all pulp-treated teeth were crowned, any pulpotomy procedure was not counted as a separate PDP.

Considering the actual amount of trauma exerted on the periodontium upon extraction, the number of root extractions rather than the number of tooth extractions was counted. Removing a multi-rooted molar may induce more pain than extracting a single-rooted one. Consequently, a maxillary molar extraction was counted as three extractions while the removal of an incisor was counted as one extraction and the removal of a rootless tooth due to normal physiologic shedding was not counted as a PDP [14].

Blinded members of the dental team were assigned to collect postoperative data in the post anesthesia-care unit where all children were monitored for vomiting, pain, swelling and time consumed from the minute of extubation to the minute the child was cleared by the blinded anesthesia assistant as fit to go home. A patient was considered ready for discharge when his/her Post Anesthesia Discharge Scoring System (PADSS) equaled 9 or higher [15] (table 1).

Upon clearance from the post anesthesia care unit, parents were prescribed "take-home Paracetamol" (10–15 mg/kg Paracetamol syrup) only when needed as per child's request. In case the child needed more than 6 doses a day, the parents were instructed to contact their pediatric dentist.

Parents were interviewed 24 hours after clearance from post anesthesia care unit and asked to report any vomiting episodes and number of times Paracetamol was needed to relief pain.

Statistical Analysis

Demographic data, time consumed from extubation to reach PADSS score 9, number of postoperative vomiting episodes and need for postoperative analgesia were statistically compared between the four groups. Using Microsoft Excel data analysis tool pack, the statistical test used was Student's *t* test for comparison of sample means. A preliminary F test for comparison of sample variances was performed to determine the appropriate t test variant to use, according to whether the sample variances were found to be equal. A *"p"* value less than 0.05 was considered significant.

Table 1. Post anesthesia Discharge Scoring System (PADSS) used in the study

1. Vital signs
2 = within 20% of preoperative value
1 = 20-40% of preoperative value
0 = 40% of preoperative value
2. Ambulation and mental status
2 = Oriented X 3 **and** has a steady gait
1 = Oriented X 3 **or** has a steady gait
0 = Neither
3. Pain, or nausea~vomiting
2 = Minimal
1 = Moderate
0 = Severe
4. Surgical bleeding
2 = Minimal
1 = Moderate
0 = Severe
5. Intake and output
2 = Has had PO fluids and voided
1 = Has had PO fluids or voided
0 = Neither

The total score is 10. Patients scoring ≥9 are considered fit for interviewing and discharge.

RESULTS

Parents of three children were not reachable, one from group O and two from group DO. Statistical analysis for demographic data including age, gender, body weight and anaesthesia time showed no significant differences between the four groups (P > 0.05), therefore, the four groups were considered comparable (table 2).

No statistically significant difference was found between groups D and DO (the groups treated with Dexamethasone alone or combined with Ondansetron) regarding post anaesthesia care unit time PACUT (P> 0.05). However, a significant longer stay in PACU was observed in the control group (C) compared to the other 3 groups (P < 0.05) (Table 2).

There was a significant reduction in postoperative vomiting (POV) episodes in treatment groups D, O and DO compared to group C (control group) P < 0.05. There was no significant difference between Dexamethasone, Ondansetron or combining them in reducing POV episodes (P> 0.05) (Table 2).

The need for postoperative Paracetamol analgesia was associated with the increase in number of painful dental procedures (PDP's). There was significant difference between the two groups treated with Dexamethasone (D and DO) compared to groups O and C (Table 2) with decreased need for postoperative analgesia in the Dexamethasone treatment groups.

Within the control group C, there was a significant difference in the incidence of POV between children who had dental extractions and children who underwent only restorative procedures without extractions (P < 0.05).

Table 2. Patient demographics and recovery profile. Data are Means ± SD or percentage (%)

	Group D	Group O	Group DO	Group C
Age; Yrs	6.03 ± 1.9	6.4 ± 1.6	6.25 ± 2	6.39 ± 1.7
Weight; Kg	22 ± 5	24 ± 7	23 ± 8	22 ± 4
Duration of anesthesia; min	94 ± 21	90 ± 25	88 ± 27	95 ± 19
PACUT in minutes	82.8 ± 3.3	84.7 ± 5.1	80 ± 3.7	105 ± 6.6*
POV in episodes	0.033 ± 0.17	0.034 ± 0.18	0.021 ± 0.14	0.33 ± 0.61
Percentage of Children who experienced POV	3.3%	2.3%	1.1%	27.16%*
Number of times Paracetamol was used				
□ 3 PDP's	1.1 ± 0.5	1.97 ± 07	1.16 ± 0.6	2.1 ± 0.5
≥ 3 PDP's	1.94 ± 0.6	3 ± 0.7**	2.1 ± 0.6	3 ± 0.7**

Group D= Dexamethasone, Group O= Ondansetron, Group DO= Dexamethasone plus Ondansetron, Group C= Control.

PDP= Painful Dental Procedure

*= Significant in C compared to D, O and DO; $p < 0.05$.

**= significant in O and C compared to D and DO; $p < 0.05$.

DISCUSSION

The present study adds child dental rehabilitation to other surgical procedures reported in current literature that require prophylaxis of PONV should DGA be carried out on children smoothly and hassle free. This goes in agreement with Splinter and Rhine in 1998 [16], Khalil *et al* in 2005 [17], Banerjee *et al* in 2014 [18]. A study conducted by de Orange *et al* in 2012 [19] reported that routine prophylaxis for PONV is unnecessary as they found no statistical difference between a study group treated with Ondansetron combined with Dexamethasone and the control group. This disagreement probably reflects the multifactorial nature of PONV etiology. The type of surgery is one contributing factor in causing PONV. De Orange [19] study was conducted on children who underwent circumcision, inguinal and umbilical hernia which were considered by the authors as surgeries with low emetic potential. Other fore mentioned studies which are in agreement with the current study were carried out on children who underwent high emetic potential surgeries such as tonsillectomies, adenoidectomies and strabismus. Where DGA lies in that scale is a subject for further investigation[16-18].

Dental treatment under general anesthesia (DGA) involves a diversity of procedures including restorative dentistry and dental extractions which may cause bleeding. In this study, restorative procedures were done and finished before extractions to avoid blood contaminating the interface between tooth surface and the adhesive restorative materials. However, this practice of postponing extractions to just-before extubation time and removal of pharyngeal pack may have allowed oozing blood to find its way to the stomach. The accumulation of blood in the stomach is reported by Kovac in 2007 [4] to stimulate serotoninergic receptors in the cortex and chemoreceptor triggering zone of the fourth ventricle leading to vomiting. On that basis, the significantly lower rate of POV observed among children who did not undergo extractions in the control group might be explained. Accordingly, the current study suggests careful control of post-extraction bleeding prior to removal of pharyngeal pack to minimize the chances for PONV. A pediatric dentist may consider prioritizing extractions while pharyngeal pack is in place and swallowing reflexes are inhibited by anesthesia if it will not affect bonding of restorative materials to the cavity walls of an adjacent tooth.

Anesthesia is considered one of the risk factors for PONV. In the current study, anesthesia was induced with sevoflurane and bolus propofol followed by sevoflurane carried with nitrous oxide oxygen was used for maintenance of anesthesia. The use of volatile anesthetics is associated with a two-fold increase in the risk of PONV, with risk increasing in a dose-dependent manner. The use of volatile anesthetics may be single most important factor for predicting emesis early in the first 2 postoperative hours [20]. Intravenous anesthesia might be better than inhalational anesthesia for early regaining of gastrointestinal motility and decreasing POV[21]. Propofol was used during induction of anesthesia in all the study group with possible reduction of the incidence of PONV, however, there is little evidence to support this claim[22].

Nitrous oxide is also known as a contributing factor for early PONV especially for those at risk[23]. However, recent ENIGMA-II trial has proved its safety in anesthesia for non cardiac surgeries with relative risk of PONV far less than previously believed[24]. Nitrous oxide did not increase the risk of death and cardiovascular

complications or surgical-site infection, the emetogenic effect of nitrous oxide can be controlled with antiemetic prophylaxis, and a desired effect of reduced volatile agent use was shown[24].

In the current study, we observed that combining Dexamethasone with Ondansetron lowers slightly the incidence of POV than using Ondansetron alone. The difference was not statistically significant. In 1998 Splinter and Rhine [15] reported that adding small dose of Dexamethasone to Ondansetron results in a highly significant reduction in PONV. The difference between the two findings might be attributed to the routine use of intraoperative analgesia in the present study which may have markedly masked PONV as reported by de Orange et al in 2012[19] and may also resulted from the complex etiology of PONV.

Despite the statistically significant difference in PACUT observed between study groups D, O, and DO in one hand compared to the control group C on the other hand, the difference was found to be of no financial significance. In the current study no child required unexpected hospitalization after DGA but the average delay in child discharge was 25 minutes per episode of vomiting. Even though we found no financial impact on treatment costs due to high incidence of POV in the control group, the current study supports the stand point that PONV is still a mishap which pediatric dentists would like to minimize its occurrence regardless of related financial aspects[25].

In the current study, there was no significant difference between Dexamethasone, Ondansetron or combining them on the prophylactic effect on PONV. However, Dexamethasone groups (D and DO) were associated with lower need for postoperative Paracetamol analgesia than both control group and Ondansetron group. There are studies by Czarnetzki *et al* in 2008[25] and Bartlett and Hartle[26] in 2013 that Dexamethasone may be associated with increased postoperative bleeding risk, postoperative infection, delayed wound healing, perioperative hyperglycaemia and adverse psychiatric effects. Putting these studies in consideration, our study cautiously supports using Dexamethasone over Ondansetron as an antiemetic agent due to its advantages being an anti-inflammatory agent that lowers the postoperative needs for analgesia.

The current study investigated the postoperative need for analgesia by interviewing parents. No reliable pain assessment tool was used which might be considered as a limitation of the study. Another limitation might be the accuracy of calculating the post anesthesia care unit time (PACUT) where the blinded anesthesia assistant decided a child reached ≥9 PASS score; a somewhat subjective observation. It might be worth noting that it gives strength to the study findings that the blinded anesthesia assistant was the same for all cases and that the current study adopted a counting system for painful dental procedures rather than counting the overall number of treated teeth.

CONCLUSIONS

Postoperative nausea and vomiting are common mishaps among children undergoing DGA making the experience of procedures unpleasant for them and distressing for the care givers. Dexamethasone could be considered as a useful adjunct in preventing PONV and reducing the need for postoperative analgesia, yet it has to be used with caution regarding its possible side effects especially in cases of DGA with multiple dental extractions. When deciding prophylaxis for postoperative nausea and vomiting, it is advisable to custom a drug profile for each child patient undergoing DGA that puts his/her medical history and the type of dental procedures to be done in mind. Our findings may help pediatric dentists to collaborate with the anesthesia team to reach decisions on the appropriate use of agents and treatment adjuncts that would help prevent unwanted postoperative sequelae of DGA.

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