"KETOFOL" IN 1:20 DILUTION PROVIDES STEADY SEDATION PHASE FOR PEDIATRIC ESOPHAGO-GASTRO-DUODENOSCOPY

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Abstract

Background: There is a boom in pediatric esophago-gastro-duodenoscopy (EGD) arising from (a) impetus for early diagnosis of pathology and (b) improved safety in the peri-anesthesia care. Still, the techniques are always being investigated to minimize anesthetics' exposure on developing brains while improving post-anesthesia recovery and procedural room turnovers.

Objective: To evaluate the anesthetic-sedative-analgesic sparing effects of very low dose ketamine-addition to propofol-sedation ("ketofol" in 1:20 dilution) for pediatric EGD.

Materials and Methods: A prospective double-blind placebo-controlled randomized study among 140 patients American Society of Anesthesiologists Physical Status Class I-III patients aged 2-12 years who presented for EGD at **p**eri-operative area of Children's Hospital. The patients were assigned to receive either ketamine-propofol solution (study group) or saline-propofol solution (control group). 10mg ketamine was added to every 200mg propofol to create 1:20 dilution. After a bolus of propofol 500mcg/kg (with or without ketamine 25mcg/kg), sedation was maintained with titrated continuous infusion of propofol 150-500mcg/kg/min (with or without ketamine 7.5-25mcg/kg/min). The following measurements were done**:** (a) Medication doses; (b) Incidence of adverse airway events; (c) Post-anesthesia care unit discharge time; (d) Pediatric Anesthesia Emergence Delirium scale scores during emergence; and (e) Children's Hospital Eastern Ontario Pain Scale scores during recovery.

Results: The median propofol dose administered was significantly less in ketamine group as compared to placebo group; only 14% patients in ketamine group required propofol "rescue" bolus as compared to 33% patients in placebo group requiring propofol "rescue" bolus. As compared to the patients who received placebo, there was a clinical trend toward less movement among the patients who received ketamine, however, it did not achieve level of significance (P=0.06). Incidence of coughing, laryngospasm and oxygen desaturation was similar among the two groups. Discharge times from hospital were similar between the two groups indicating that "ketofol" in 1:20 dilution did not delay patients' discharge in fast-track one-phase recovery protocol, but rather,

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it shortened their postoperative stay in standard two-phase recovery protocol. The post-anesthesia recovery scales were similar between the two groups.

Conclusions: During pediatric EGD, "ketofol" in 1:20 dilution decreased the dose requirements of propofol and improved the quality of sedation without affecting the patients' recovery and discharge to home.

Keywords: ketamine; propofol; endoscopy, digestive system; anesthesia; pediatrics; apnea.

Introduction

There is a boom in pediatric esophago-gastro-duodenoscopy (EGD)[1-2] arising from (a) impetus for early diagnosis of pathology and (b) improved safety in the peri-anesthesia care. Still, the techniques are always being investigated to minimize anesthetics' exposure on developing brains while improving post-anesthesia recovery and procedural room turnovers.

Anesthesia care providers across the world[3-15] have published their experiences with various combinations of sedative medications to achieve best conditions for EGD at their institutions. The anesthetic-sedative protocol that has emerged triumphant across the board is propofol sedation which has become the norm in both pediatric and adult patient population undergoing EGD. At our institution, some practitioners add ketamine to create "ketofol": a premixed solution of ketamine and propofol. Therefore, the aim of this study was to evaluate the anesthetic-sedative-analgesic sparing effects of ketamine-addition to propofol-sedation for pediatric EGD.

Materials and Methods

After institutional review board approval and signed written informed parental consent (plus oral patient assent from patients aged 7 years and above), a prospective double-blind placebo-controlled randomized study was conducted to measure the efficacy and the quality of peri-anesthesia care when ketamine was added to propofol infusion during EGD. The American Society of Anesthesiologists Physical Status (ASA PS) Class I-III pediatric patients aged 2-12 years were eligible. The ASA PS IV-V patients, and the patients with serious impairment of respiratory, cardiovascular, hepatic, renal, neurological or endocrine functions, or those with known allergies to lidocaine, propofol, glycopyrrolate, eggs, ketamine or sevoflurane were excluded from the study.

Patients were anesthetized by inhalational induction with 8% sevoflurane in oxygen and nitrous oxide mixture. Subsequently, intravenous cannula was inserted and sevoflurane was discontinued. The patients received intravenous glycopyrrolate (0.01mg/kg) to dry oral secretions, and 4% lidocaine spray (4mg/kg) into the upper airways using laryngotracheal topical anesthesia (LTA) kit and laryngoscope after adequate depth of anesthesia had been achieved. Standard ASA monitoring was used.

The patients were assigned to receive either ketamine-propofol solution (study group) or saline-propofol solution (control group) for which the anesthesia-providers were blinded. Per pharmacy compounding, 10mg ketamine was added to every 200mg propofol to create 1:20 dilution. After a bolus of propofol 500mcg/kg (with or without ketamine 25mcg/kg), sedation was maintained with titrated continuous infusion of propofol 150-500mcg/kg/min (with or without ketamine 7.5-25mcg/kg/min).

During the peri-anesthesia period, the following were recorded: (a) demographics; (b) peri-operative times; (c) vital signs; (d) medication doses; (e) incidence of adverse airway events; (f) wake-up time as per electronic medical record (EMR); (g) post-anesthesia care unit (PACU) discharge time (from phase I and/or phase II) as recorded in EMR; (h) the Pediatric Anesthesia Emergence Delirium (PAED) scale[16] scores during emergence; and (i) the Children's Hospital Eastern Ontario Pain Scale (CHEOPS)[17] scores during recovery.

Statistical Analysis

For sample size calculation with continuity correction, we hypothesized that as compared to 50% patients in control group (saline-propofol), only 25% patients in study group (ketamine-propofol) would need additional propofol boluses during pediatric EGD. Based on proportional difference of 25% between the two groups, the minimum sample size of 132 with 66

patients per group was required to provide adequate statistical power (1-beta error) at 80% limiting alpha error at 5%. To compensate for the risk of certain cases getting withdrawn or eliminated during the analysis, the finally chosen sample size was 140 with 70 patients per group to maintain adequate statistical power. Medians with 95% confidence intervals[18] were calculated as measures of central tendency for the demographics, parameters, medications, and times, and were compared between the study and control groups by Mann-Whitney U test calculator. The proportions were compared by 2x2 contingency table and evaluated for Fisher exact test to calculate P-value. P<0.05 was considered significant. The primary outcome was the dose of propofol (and its boluses). The secondary outcomes were stability of vital parameters, incidence of adverse airway events, quality of emergence as per scores, and times to discharge.

Results

Among the 140 patients enrolled one patient was excluded due to incomplete data collection. Age, weight and gender were similar between the two groups. The median propofol dose administered was significantly (P<0.01) less in ketamine group as compared to placebo group (Table 1); only 14% patients in ketamine group required propofol "rescue" bolus as compared to 33% patients in placebo group requiring propofol "rescue" bolus (P=0.01). Fentanyl administrations were similar between the two groups: 6% patients in ketamine group and 9% patients in placebo group required fentanyl. As compared to the patients who received placebo, there was a clinical trend toward less movement among the patients who received ketamine, however, it did not achieve level of significance (P=0.06). Overall incidence of coughing

Table 1
Demographics and Intraoperative Characteristics of Patients
95% Confidence Intervals In Parentheses (Lower bound, Upper bound)

	KETAMINE GROUP (n=70)	PLACEBO GROUP (n=69)	P- Value
Median Age (years)	8 (6, 9)	8 (6, 10)	0.34
Median Weight (kilograms)	28 (23, 33)	30 (25, 34)	0.36
Percentage of Female Patients	41%	54%	0.18
Median Time From Propofol Start To EGD Start (minutes)	4 (4, 4)	4 (3, 5)	>0.99
Median Time From EGD Start To EGD/ Propofol End (minutes)	6 (6, 6)	6 (5, 7)	0.31
Median Time for Total Propofol Delivery (minutes)	10 (9, 11)	11 (10, 12)	0.45
Percentage of Patients Who Required Propofol Boluses	14%	33%	**0.01**
Median Propofol Administered (mg/kg/min)	0.168 (0.14, 0.196)	0.253 (0.218, 0.288)	**<0.01**
Percentage of Patients Who Required Fentanyl	6%	9%	0.53
Percentage of Patients Who Moved During EGD	13%	26%	0.06
Percentage of Patients Who Coughed During EGD	7%	9%	0.76
Percentage of Patients Who Had Laryngospasm	0	1%	0.5
Percentage of Patients Who Had Oxygen Saturation <90%	0	1%	0.5

EGD: Esophago-gastro-duodenoscopy.

was common (8%) but laryngospasm and oxygen desaturation was uncommon (<1%); however, their incidence was similar among the two groups (Table 1). Vital signs' trends were similar between the two groups (Table 2-3). No patient required endotracheal intubation. The post-anesthesia recovery scales (the PAED scale scores and the CHEOPS scores) were similar between the two groups (Table 4). Discharge times from hospital were similar between the two groups indicating that "ketofol" in 1:20 dilution did not delay patients' discharge in fast-track one-phase recovery protocol, but rather, it shortened their postoperative stay in standard two-phase recovery protocol.

Discussion

The addition of ketamine to propofol ("ketofol" in 1:20 dilution) for pediatric EGD resulted in significantly decreased propofol dose requirements without affecting patients' discharge to home. Additionally, there were trends towards decreased need for "breakthrough (top-up)" boluses of sedatives and less movement during EGD with "ketofol" in 1:20 dilution.

Addition of a second anesthetic-sedative reduces the dosage requirements for both medications, demonstrating additive or synergistic effect on the brain. Therefore the observation of reduced total dose requirements of propofol in our study group was expected. However, the clinically relevant reduction of "breakthrough (top-up)" boluses and patients' movements in our study group asserts that continuous "ketofol" provided more homogeneous sedation phase as compared to continuous propofol for pediatric EGD despite not achieving the level of statistical significance. These effects can be secondary to the analgesic effects of ketamine as an anesthetic-sedative. Interestingly, the vital signs did not change significantly irrespective of ketamine addition, apparently because, the dose of ketamine as a sympathomimetic in 1:20 dilution "ketofol" was too low to express ketamine-related tachycardia and hypertension. The absence of significant differences in fentanyl requirements between the two groups can be secondary to the higher total dose of propofol in the control group wherein propofol as a sedative could have masked the patients' need for analgesia in ultra-short duration pediatric EGD (median 6 minutes duration in both groups). As such in spite of "ketofol" looking good clinically, addition of ketamine to propofol may appear unwarranted for ultra-short duration procedures. However, since the insertion of endoscopes during EGD in non-intubated pediatric patients with unprotected airways is a high risk for airway compromise during inadequate depth of sedation-anesthesia, the smoother sedation phase with "ketofol" outweighs the time needed to add ketamine

Table 2
Patients Wherein Vital Parameters Were Available For At Least 5-minutes Post-Induction.
95% Confidence Intervals in Parentheses (Lower bound, Upper bound)

	KETAMINE GROUP (n=62)	PLACEBO GROUP (n=60)	P- Value
Median Percent Change At Induction From Baseline Preoperative Values			
Heart Rate	20% (11%, 29%)	17% (8%, 27%)	0.97
Systolic Blood Pressure	-5% (-8%, -1%)	-8% (-15%, -2%)	0.18
Diastolic Blood Pressure	-22% (-28%, -17%)	-21% (-30%, -13%)	0.63
Median Percent Change 5-min-Post-Induction From Baseline Preoperative Values			
Heart Rate	24% (14%, 35%)	22% (16%, 28%)	0.98
Systolic Blood Pressure	-5% (-9%, -2%)	-7% (-12%, -3%)	0.41
Diastolic Blood Pressure	-21% (-30%, -11%)	-22% (-31%, -13%)	0.81

Table 3
Patients Wherein Vital Parameters Were Available For At Least 10-minutes Post-Induction.
95% Confidence Intervals In Parentheses (Lower bound, Upper bound)

	KETAMINE GROUP (n=55)	PLACEBO GROUP (n=51)	P- Value
Median Percent Change At Induction From Baseline Preoperative Values			
Heart Rate	20% (8%, 31%)	16% (6%, 26%)	0.98
Systolic Blood Pressure	-5% (-9%, -1%)	-9% (-15%, -2%)	0.13
Diastolic Blood Pressure	-25% (-29%, -20%)	-22% (-31%, -12%)	0.72
Median Percent Change 5-min-Post-Induction From Baseline Preoperative Values			
Heart Rate	21% (6%, 35%)	21% (17%, 25%)	0.98
Systolic Blood Pressure	-6% (-10%, -2%)	-8% (-12%, -3%)	0.33
Diastolic Blood Pressure	-25% (-33%, -17%)	-24% (-31%, -17%)	0.62
Median Percent Change 10-min-Post-Induction From Baseline Preoperative Values			
Heart Rate	28% (18%, 38%)	29% (22%, 36%)	0.64
Systolic Blood Pressure	-1% (-5%, 4%)	-5% (-11%, 1%)	0.15
Diastolic Blood Pressure	-22% (-29%, -14%)	-15% (-23%, -6%)	0.98

to propofol for ultra-short duration procedures like pediatric EGD. Finally, the emergence parameters and wake-up times being similar between the two groups can be interpreted as either (a) low dose ketamine as an additive does not interfere or delay the emergence from propofol; or (b) low dose ketamine analgesia does not hasten or improve the quality of recovery. During the study enrollment period over the years, pediatric EGD patients' discharge protocol at our institute evolved from standard two-phase recovery protocol to fast-track one-phase recovery protocol. Herein, the significant early discharges with "ketofol" during standard two-phase may be explained as discharging criteria in PACU-II being more akin to patients' absolute readiness to go home as compared to discharging criteria assessed by fast-track nursing staff in PACU-I being more akin to rapid turnover. Alternately, the improved quality of recovery from "ketofol" combining analgesia of ketamine with lower propofol dose was appreciable in PACU-II wherein patients were being discharged at least one-hour post-sedation.

Our study, which demonstrated reduced propofol dose despite very low dose ketamine (1:20 dilution "ketofol") with overall uncommon airway complications, contrasts with the available medical literature. Green et al (2001)[19] reported ketamine as a sole agent used for 636 pediatric gastroenterology procedures that included 548 pediatric EGD. The first ketamine dose was 1mg/kg with total median ketamine dose being 1.34mg/kg wherein airway complications were very common (>10%) with laryngospasm being common complication in 9.5% pediatric EGD patients. Similarly, Thakkar et al (2007)[20] reported 239 out of 10,236 as complicated pediatric EGD (and hence a common adverse occurrence with incidence being >1%) with two-thirds complications being reversible hypoxia; 72% of the complications occurring in the sedated patients as compared to 28% of the complications occurring in the general anesthesia patients (adjusted odds ratio 5.33) led to intravenous sedation being named as a risk factor for complicated pediatric EGD. Lightdale et al (2008)[21] reported in American Society of Gastrointestinal Endoscopy

Table 4
Postoperative Characteristics of the Patients.
95% Confidence Intervals In Parentheses (Lower bound, Upper bound)

WHEN PATIENTS WERE DISCHARGED FROM PACU-I ITSELF (FAST-TRACK ONE-PHASE RECOVERY PROTOCOL)			
	KETAMINE GROUP (n=46)	PLACEBO GROUP (n=45)	P- Value
Median Time From Propofol End To EMR Documented Wake-Up Time (in minutes)	28 (23, 33)	27 (23, 31)	0.33
Median Time From Propofol End To PACU-I Discharge Readiness (in minutes)	53 (48, 58)	49 (45, 53)	0.19
WHEN PATIENTS WERE DISCHARGED FROM PACU-II AFTER PACU-I (STANDARD TWO-PHASE RECOVERY PROTOCOL)			
	KETAMINE GROUP (n=24)	PLACEBO GROUP (n=24)	P- Value
Median Time From Propofol End To EMR Documented Wake-Up Time (in minutes)	23 (16, 30)	31 (15, 46)	0.16
Median Time From Propofol End To PACU-I Discharge Readiness (in minutes)	31 (26, 36)	34 (26, 41)	0.58
Median Time From Propofol End To PACU-II Discharge	77 (63, 90)	99 (89, 109)	**<0.01**
	KETAMINE GROUP (n=70)	PLACEBO GROUP (n=69)	P- Value
Median PAED Scale @ 0-min	12 (12, 12)	12 (12, 12)	0.18
Median PAED Scale @ 10-min	12 (12, 12)	12 (12, 12)	0.35
Median PAED Scale @ 20-min	6 (4, 8)	6 (1, 11)	0.9
Median CHEOPS Scale @ 0-min	6 (6, 6)	6 (6, 6)	0.96
Median CHEOPS Scale @ 10-min	6 (6, 6)	6 (6, 6)	0.87

PACU: Post-Anesthesia Care Unit
EMR: Electronic Medical Record
PAED: Pediatric Anesthesia Emergence Delirium
CHEOPS: Children's Hospital Eastern Ontario Pain Scale

(ASGE) journal that, during pediatric EGD, propofol sedation supervised by anesthesia providers hastens the induction of sedation (by 21%) but delays the discharge (by 46%) thus increasing the total time (by 29%) as compared to midazolam-fentanyl sedation supervised by gastroenterologists. Moreover, Dosani et al (2010)[22] reported that 4mg/kg propofol given slowly over 3minutes to 6-15years old children presenting for gastrointestinal endoscopy sustained patients' spontaneous breathing; however, the longer duration of slower propofol administration during the study period resulted in 30% patients requiring additional top-up doses of sedatives, while 14% patients had insufficient breathing with decreased tidal volumes, respiratory rates and capnograms. Tosun et al (2007)[23] added 1mg/kg ketamine to 1.2mg/kg propofol to induce better sedation than propofol-fentanyl. Barbi et al (2003)[24] reported about decreased propofol-injection pain with 0.5mg/kg ketamine. However, due to limited overall medical evidence favoring "ketofol", van Beek and Leroy (2012)[25] could only conclude limited role of ketamine just as a preemptive analgesic against propofol-injection pain. Recently, Patino et al (2015)[26] revived the question that non-intubated patients were

more likely to suffer respiratory problems as compared to the intubated patients when pediatric EGD was being performed with propofol sedation-anesthesia. Biber et al (2015)[27] concluded that age ≤5years, ASA PS >1, co-morbidity (lower respiratory tract inflammation and obesity) and EGD as a procedure itself increase the risk for respiratory complications primarily performed under propofol sedation primarily administered by the pediatric intensivists in 12,030 gastrointestinal endoscopies.

Our study has some limitations. It would have been better if we had defined apnea as oxygen saturation <90% or absent respiratory movements with absent capnogram ≥20seconds (as similar to Dosani et al (2010)[22]), instead of presuming apnea as the need for bag-mask ventilation. However, there is always potential risk to lose the capture of capnogram from the side-port of nasal oxygen cannula when the patients' mouths are opened for EGD.

Conclusion

During pediatric EGD, "ketofol" in 1:20 dilution decreased the dose requirements of propofol and improved the quality of sedation without affecting the patients' recovery and discharge to home.

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