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Period Prevalence of Ketamine-Propofol Admixture “Ketofol” in the Operating Room among Anesthesia Providers at an Academic Medical Center

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Background: The primary aim of this study was to determine the period prevalence of the single-syringe ketamine-propofol admixture used for sedation and induction among anesthesia providers during a 5-year period before and after educational sessions addressing barriers to its use. Secondary aims were to determine barriers to its use and address the most prevalent concerns through educational sessions.





Material/Methods: Surveys were administered to certified and student registered nurse anesthetists, anesthesia residents, and anesthesiologists at Mayo Clinic Rochester, MN before and after educational sessions addressing common barriers. Identified barriers were addressed by oral and/or electronic presentations with identical content.

Results: Pre-education period prevalence for sedation was 110 (43%) and 64 (25%) for induction. Identified barriers were uncertainty of benefit in 62 respondents (23%), mixed controlled substance disposal in 48 (18%), regulatory/institutional policies in 20 (7%), and compatibility in 9 (3%). Post-education period prevalence for sedation was 102 (44%), and induction 63 (27%). No concerns were noted in 72% of the post-education group versus 42% in the pre-education group ($p < 0.01$). No concerns were reported in 51% of the electronic only education group versus 64% in the oral education group ($p < 0.01$).

Conclusions: The period prevalence of “ketofol” was greater for sedation than induction. The period prevalence following education showed a slight increase in both sedation and induction use. There was a significant reduction in barriers following education, with oral presentations being more effective than electronic only. Period prevalence was increasing following education; however, allowing more time may have shown a significant practice change.

MeSH Keywords: **Anesthesia • Drug Therapy, Combination • Ketamine • Operating Rooms • Prevalence • Propofol**

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/893944>

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Background

Propofol is an extensively used intravenous induction agent. Its mechanism of action may involve facilitation of inhibitory neurotransmission mediated by gamma-Aminobutyric acid [1]. Due to its rapid redistribution, it is an ideal induction agent, but is associated with hypotension and respiratory depression. Ketamine is infrequently used as a primary induction agent and is more often used for its analgesic and sedative properties. Ketamine is an N-methyl-D-aspartate receptor antagonist that causes a dissociative state. In sharp contrast to other anesthetic agents, ketamine increases arterial blood pressure, heart rate, and cardiac output [1]. In recent years, the combination of ketamine and propofol ("ketofol") has been used mainly for the purpose of sedation. This admixture has been used primarily to counterbalance, or offset, the adverse effects exhibited when the medications are administered individually.

There has been minimal research conducted on "ketofol" used as a sedative or induction agent among anesthesia providers in the operating room. Research that has been conducted focused primarily on sedation in the emergency room, with few studies in the operating room [2–9]. The use of single-syringe "ketofol" in a 1:1 ratio for sedation and analgesia of adults in the emergency department resulted in quick recovery, few adverse events, and patient and staff satisfaction [2]. An investigation of the co-administration of ketamine and propofol, as compared to fentanyl and versed, for procedural sedation and analgesia in the emergency department concluded that this combination provided adequate sedation and analgesia, less oxygen desaturation, and a deeper level of sedation [6]. Recently, it was demonstrated that "ketofol", delivered as an infusion for deep sedation in the operating room, appears to be a safe and effective anesthetic technique [7]. Furthermore, during awake craniotomies, "ketofol" provided hemodynamic stability without intraoperative episodes of increased intracranial pressure [8]. In addition, "ketofol" infusion in a critical care and procedural setting has demonstrated a number of benefits including airway preservation, maintenance of spontaneous respiration, hemodynamic stability, analgesia, and rapid recovery [9,10].

Ketamine and propofol in a single-syringe are reported to create an admixture used for balancing cardiorespiratory effects during induction of general anesthesia. When propofol alone was compared to this combination, it resulted in a decrease of >20% of systolic blood pressure from baseline at 5 minutes and 10 minutes after administration. The dosage of "ketofol" used when comparing these induction agents was 0.75 mg/kg of ketamine and 1.5 mg/kg of propofol, respectively, but there are a variety of dosing variations that have been used to create this admixture [11]. Based on a study performed in 1995, the effective dose (ED₅₀) of propofol and ketamine in combination

was identified as 1.05 mg/kg and 0.35 mg/kg for anesthesia, with the sedative and anesthetic effects being additive [12]. Thus, despite the safety and apparent improved outcomes of the admixture, very little evidence exists for its use as a sedative or an induction agent among anesthesia providers in the operating room.

Given the increasing use of this medication combination in the last decade, the primary aim of the present study was to determine the period prevalence of single-syringe ketamine propofol admixture used for sedation and induction among anesthesia providers within the last 5 years prior to and following educational sessions. Secondary aims included assessing perceived hemodynamic stability, concerns regarding the combination, previous education, type of provider, and years of anesthetic experience, but mainly focused on determining barriers to use and addressing the most prevalent concerns through educational sessions.

Material and Methods

The present study was deemed exempt from the institutional review board at Mayo Clinic Rochester, Minnesota. All providers gave consent.

Study population

The study population consisted of all anesthesia providers either in-training or post-training at Mayo Clinic Rochester, Minnesota during the months of November 2013 through March 2014. Demographic data of the providers was obtained via indirect contact of a survey. Mayo Clinic is a tertiary academic medical center with approximately 500 anesthesia providers comprising 130 anesthesiologists, 260 certified registered nurse anesthetists (CRNA), 50 anesthesia residents, and 50 student registered nurse anesthetists (SRNA).

Intervention

A pre-survey was created to investigate the period prevalence and barriers to use of "ketofol" administration in the last 5 years. Themes that were identified on the pre-education survey served as the foundation for educational material that was then subsequently presented to anesthesia providers. A similar post-education survey was administered to the anesthesia providers to evaluate whether the educational material had any impact on the prevalence of the admixture.

Barriers to the use of "ketofol" identified on the pre-survey guided education, which was either a PowerPoint presentation distributed via email or PowerPoint presentation presented in-person. Although the approach of education was

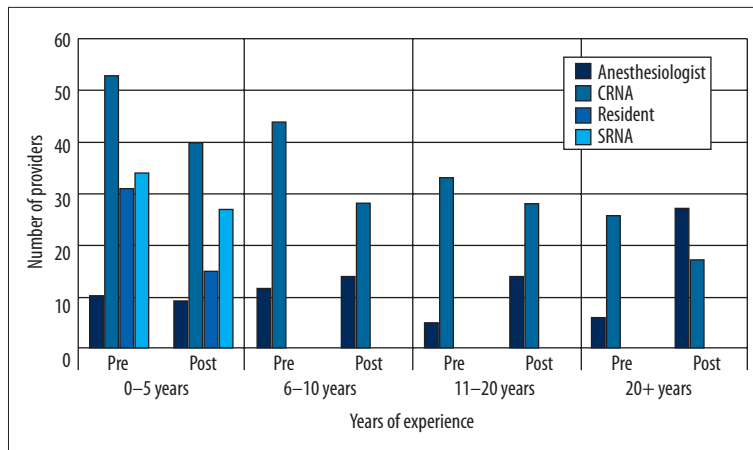


Figure 1. Demographic representation of anesthesia providers at an academic medical center by title and years of anesthesia experience.

different, the PowerPoints contained identical content. The in-person sessions, approximately 15 minutes in length, were presented to the CRNAs and SRNAs. The PowerPoint presentation was emailed to all anesthesia providers. The post-education survey was distributed 1 month after the completion of education. These surveys consisted of qualitative and quantitative questions, and were developed with the Mayo Clinic Survey Research Center. The surveys were mainly closed-ended questions with 1 open-ended and 1 Likert scale question. Functionality and validity was pilot tested prior to distribution via Research Electronic Data Capture (Redcap), which is a web-based data collection system. This pilot test included 15 anesthesia providers with a mix in provider type. Of these pilot test surveys, 5 responses were obtained prior to distribution to the study population. Each survey was active for 1 month, with weekly completion reminders distributed via email. The providers included anesthesiologists, CRNAs, anesthesia residents, and second- and third-year SRNAs. Please refer to Appendix 1 for a copy of the pre- and post-survey that was utilized during the study.

Statistical Methodology

Of the approximate 500 anesthesia providers receiving the survey, an estimated 250 surveys were expected to be completed. This estimated percentage of anesthesia providers provides a precision of $\pm 5.5\%$ base on the half width of the 95% confidence interval. The primary outcome was to determine the period prevalence of single-syringe “ketofol” both as a sedative and as an induction agent in the operating room in the last 5 years. Secondary outcomes were to determine barriers and to assess educational effectiveness. Continuous measurements are expressed as mean \pm standard deviation (SD) or median and interquartile range (IQR) where appropriate. Categorical variables are reported as counts and percentages. For continuous variables, unpaired t-tests were used for parametric distributions and Mann-Whitney U tests for non-parametric distributions. For categorical variables, a the chi-square test was

used for parametric distributions and Fisher’s exact test, when applicable, for non-parametric distributions. Statistical comparisons are not reported for the primary aim because this is a descriptive study by nature. To assess educational effectiveness between the pre-survey and post-survey groups, last value carried forward imputation was utilized for missing data on some variables as a comparison of pre- versus post-educational groups with chi-square tests for statistical significance. All reported p-values are 2-tailed, and a p-value ≤ 0.05 was considered statistically significant. The JMP Statistical Package 9.0 (SAS Institute Inc, Cary, NC) was used for all calculations.

Results

Study population

Pre-education survey

There were a total of 275 respondents out of 442 potential participants (62%). Twenty-two surveys had incomplete data, leaving 253 completed surveys (57%). The study population consisted of 157 (62%) CRNAs, 34 (13%) SRNAs, 33 (13%) anesthesiologists, and 31 (12%) anesthesia residents. Out of a total 253 responses, 127 (50%) indicated they had 0–5 years of anesthetic experience, 56 (22%) had 6–10 years, 70 (28%) had greater than 10 years of experience, excluding 22 due to missing years of anesthesia training. Out of a total of 265 respondents, 99 (37%) indicated they had previous education on current knowledge or practice of the admixture (Figure 1).

Post-education survey

There were a total of 233 respondents out of 500 potential participants (46%). Of the respondents, 126 (54%) were from CRNAs, 63 (27%) from anesthesiologists, 27 (12%) from SRNAs, and 17 (7%) from anesthesia residents. Ninety-one respondents had 0–5 years of anesthetic experience (39%), 56 (24%)

Table 1. Period prevalence of ketamine-propofol admixture, “ketofol”, administered as a sedative and induction agent during the period of 2010–2014 among anesthesia providers by years of experience before and after education sessions.

	Anesthesiologist		CRNA		Resident		SRNA	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
0–5 years of experience								
Sedation [n=63 (pre), 56 (post)]	6 (9)	7 (13)	36 (57)	31 (55)	8 (13)	9 (16)	13 (21)	9 (16)
Induction [n=39 (pre), 39 (post)]	5 (13)	7 (18)	20 (51)	20 (51)	6 (15)	7 (18)	8 (21)	5 (13)
>5 years of experience								
Sedation [n=51 (pre), 46 (post)]	8 (16)	19 (41)	43 (84)	27 (59)				
Induction [n=25 (pre), 24 (post)]	6 (24)	12 (50)	19 (76)	12 (50)				

CRNA – certified registered nurse anesthetist; SRNA – student registered nurse anesthetist

had 6–10 years of experience, and 86 (37%) had greater than 10 years of experience. One hundred and twenty-one respondents (52%) indicated that they had previous education regarding the practice and/or current knowledge of the combination of ketamine and propofol (Figure 1).

Period prevalence of single-syringe “ketofol” for sedation and induction

Pre-education survey

Among the 253 completed surveys, the period prevalence of single-syringe ketamine-propofol admixture used for sedation in the last 5 years was 110 (43%). The period prevalence of single-syringe ketamine-propofol admixture used as an induction agent was 64 (25%) (Table 1 and Figure 2). Of those who had 0–5 years of anesthesia training, 39 (31%) had used the combination as an induction agent in the last 5 years. When asked about the stability of the combination as an induction agent, 20 (51%) stated that the combination was stable, and 17 (44%) rated it as very stable. Of those who had greater than 5 years of experience, 25 (20%) had used the combination as an induction agent in the last 5 years. When asked about the stability of the combination as an induction agent, 15 (60%) stated the combination was stable and 10 (40%) rated it as very stable.

Post-education survey

Among the 233 completed surveys, the period prevalence of single-syringe ketamine-propofol admixture used for sedation in the last 5 years was 102 (44%). The period prevalence of single-syringe ketamine-propofol admixture used as an induction agent was 63 (27%) (Table 1 and Figure 2). In reference to sedation, 56 (55%) of the respondents had 0–5 years of anesthetic experience, as compared to 46 (45%) that had greater than 5 years of experience. For use as an induction agent, 39

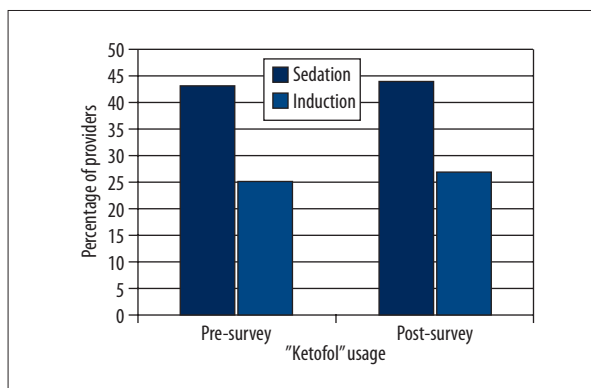


Figure 2. Period prevalence of ketamine-propofol admixture use before and after education.

(62%) had 0–5 years of anesthetic experience as compared to 24 (38%) who had greater than 5 years of experience. For the participants who indicated they had used the admixture as an induction agent, 39 (62%) rated the hemodynamic profile of the admixture as stable and 23 (37%) rated it as very stable hemodynamically.

The post-survey respondents were stratified by those with 0–5 years of experience and those with greater than 5 years of experience. The group with 0–5 years of anesthetic experience used the admixture 56/92 (60%) as compared to 46/141 (32%) in the group with greater than 5 years of anesthetic experience (RR (95% CI); 1.90 (1.41–2.55); p-value ≤0.01).

Preferred ratio of admixture

Pre-education survey

The majority preferred a 1:1 mixture of propofol and ketamine respectively, with 10:1 being the second most prevalent dose ratio in those who had 0–5 years of anesthesia experience. For those who had greater than 5 years of anesthesia experience,

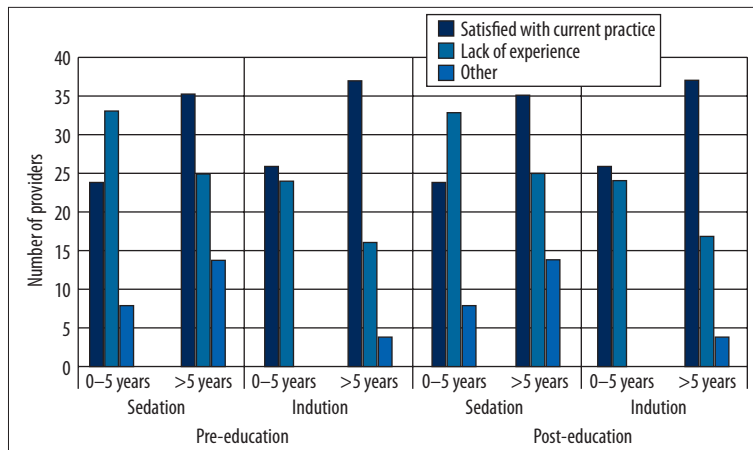


Figure 3. Reasons for not administering single-syringe ketamine-propofol admixture for sedation and induction by years of experience among anesthesia providers.

the majority preferred a 10:1 mixture of propofol and ketamine, with a 1:1 mixture the second most prevalent dose ratio.

Post-education survey

When asked about admixture concentrations, various responses were obtained. However, the most common dose ratio preferred in those with 0–5 years of experience was 1:1. In respondents who had greater than 5 years of experience, a ratio of 2:1 mixture of propofol and ketamine was the most preferred.

Reasons for not administering single-syringe “ketofol” for sedation and induction

Pre-education survey

Of those who had 0–5 years of anesthesia experience, 65 (51%) respondents stated they had not used the combination as a sedative in the last 5 years. When asked why they have not used the combination, 24 (37%) indicated they were satisfied with current practice, 33 (51%) indicated lack of experience and/or knowledge of acceptability of the combination, and 8 (12%) indicated “other”, which was most commonly reported as physician preference. Of those who had greater than 5 years of anesthesia experience, 74 (59%) respondents indicated they had not used the combination as a sedative in the last 5 years. When asked why they have not used the combination, 35 (47%) indicated they were satisfied with current practice, 25 (34%) indicated lack of experience and/or knowledge of acceptability of the combination, and 14 (19%) indicated “other”, which was most commonly related to the ability to use separately, issues with wastage, physician preference, and lack of awareness of the combination.

Of the 57 anesthesia providers with 0–5 years of experience who indicated they had not used the combination as an induction agent, the primary reason listed was “satisfied with current practice of giving only one”, 26 (46%). The next most

common reason was lack of experience and/or knowledge, 24 (42%). Of the 58 anesthesia providers with greater than 5 years of experience who had not used the combination as an induction agent, 37 (64%) indicated they were satisfied with current practice of giving only 1 at a time. The next most common reason 17 (29%) was lack of experience and/or knowledge, and 4 (7%) indicated it was too time consuming (Figure 3).

Post-education survey

Out of 233 respondents, 131 (56%) stated they had not used the combination as a sedative. This included 36 (27%) with 0–5 years of experience and 95 (73%) with greater than 5 years of experience. The most common reasons cited for not using the admixture as a sedative included satisfied with current practice of giving only 1 at a time 64 (49%), lack of experience or knowledge regarding the admixture 50 (38%), and “other”, with the most frequent reason being “individualized dosing is much safer than fixed dosing” 17 (13%).

Out of 233 respondents, 170 (73%) indicated they had not used the combination as an induction agent. This included 70 (41%) respondents with 0–5 years of experience as compared to 100 (59%) with greater than 5 years of experience. The most common reasons cited for not using the admixture as an induction agent included satisfied with current practice of giving only 1 at a time (92 respondents [54%]), lack of experience or knowledge regarding the admixture (44 respondents [26%]), and “other”, with the most common reason as “too time consuming” (34 respondents [20%]) (Figure 3).

Barriers

Pre-education survey

Of the 271 respondents who answered the question, “do you have concerns with the use of combination of ketamine and propofol”, 113 (42%) respondents had no concerns, 9 (3%) had

issues with compatibility, 62 (23%) were uncertain about the benefit of using the 2 drugs together, 9 (3%) indicated that it was not approved by the Food and Drug Administration, 11 (4%) indicated it was not approved by the institution and/or department, and 48 (18%) indicated they were unsure of how to properly dispose of mixed controlled substances. The remaining 19 (7%) indicated "other", with the most common being ability to titrate separately, concern for emergence delirium, knowledge and/or experience with combination, and unsure of dosages (Figure 4).

Post-education survey

Out of 233 respondents, 167 (72%) had no concerns. Of the 66 (28%) who stated they had concerns with the admixture, 44 (67%) stated they were uncertain about the benefit of using the 2 drugs together, with 17 (26%) indicating they were unsure of how to properly dispose of mixed controlled substances. The remaining 5 (7%) indicated they had concerns regarding compatibility of the 2 drugs (Figure 4).

Education effectiveness

The effect of education was assessed using carry forward imputation for missing values to compare pre-education and post-education groups. No concerns with the combination were noted in 72% (196/271) of the post-education group compared to 42% (113/271) of the pre-education group (RR (95% CI); 1.90 (1.64–2.21); p-value <0.01). Given that the educational material was presented differently between anesthesia providers, the post-education group was stratified into electronic education only versus oral + electronic education to determine if there was a difference in educational effectiveness. The electronic education group had more concerns compared to the education group that also had oral presentations (49% vs. 36%, RR (95% CI); 4.17 (3.17–5.49); p-value <0.01).

Discussion

Following completion of this study, it was found that period prevalence of "ketofol" was higher for sedation than induction. Although the period prevalence did not significantly change following education (averaged to be 43.5% for sedation and 26% for induction), the period prevalence did trend up. Current literature on the use of "ketofol" has only recently become apparent in the operating room. Because this admixture is relatively new and unconventional, the period prevalence revealed to be higher than anticipated. Furthermore, the anesthesia providers with less than 5 years of experience reported increased use for both sedation and induction compared to those with greater than 5 years. With years of anesthetic experience influencing possible use of the admixture, we stratified the groups

by years of experience and found the difference to be statistically significant, favoring use by novice providers.

Another interesting finding was that most anesthesia providers with fewer than 5 years of experience preferred an equal dosing ratio between ketamine and propofol. Those with greater than 5 years of anesthesia experience preferred less ketamine and more propofol initially, but after education reported a more equal ratio. This finding is congruent with more recent studies demonstrating equivalent dosing between the 2 drugs [5,11]. A potential indicator for this dosing ratio is the desired level of hemodynamic stability that was apparent in the survey results. The perception that the admixture was hemodynamically stable to very stable was detected in over 95% of the respondents. Hemodynamic stability may be more desirable than the worrisome consequence of emergence delirium, which seems to be less prevalent according to several studies [2,5,11,13].

The results of the remaining respondents that did not use the admixture revolved around 2 key issues: reluctance to accept an alternative anesthetic practice technique and lack of knowledge and/or experience regarding "ketofol". The remarkable number of respondents who reported lack of knowledge as a reason supported the need for education. Out of the total respondents in the pre-education survey, 91% said they would be "very likely" or "somewhat likely" to attend an educational session regarding the current practice of using "ketofol". Despite the large percentage of respondents satisfied with current practice, the majority would be interested in learning more regarding the admixture.

Education was tailored to address the barriers identified on the pre-education survey and resulted in a reduction of noted barriers on the post-education survey. The education had a statistical impact on the concerns regarding the admixture. From our analysis, the educational material was effective as shown by decreased concerns and increasing prevalence, but significantly more so with oral presentations versus content distributed electronically only. Web-based and face-to-face education has proven to be effective if required or mandatory. These forms of education have been studied in both nursing and other medical professions, with similar conclusions. The similarity in this evidence was the mandatory requirement to complete either form of education [14,15]. In the current study, neither education avenues were mandatory; therefore, participation could not be assessed. The group receiving oral education (and therefore known participation) had a reduction in concerns compared to the electronic education group. Our results indicate that if either form of education is not mandatory, oral education is more effective.

The current study has several limitations. The surveys only captured approximately half of the anesthesia providers; therefore, we cannot exclude non-respondent bias in our study. To reduce

non-respondent bias, survey reminders were sent out weekly for those participants who did not fill out the survey. Second, we utilized a survey that had not been previously validated from prior literature. Some questions were subject to provider perception whereas others were more objective in nature. In addition, some questions were slightly ambiguous. Although there is no evidence regarding the prevalence of “ketofol” use among anesthesia providers, our survey was designed with the assistance of the Survey Research Center at Mayo Clinic and therefore did not represent questions drafted solely by the authors. Moreover, we feel that the reliability of the survey was acceptable because the functionality was tested on a random sample of anesthesia providers prior to implementation. Third, the study population was academic anesthesia providers at a single institution and may not represent the prevalence or views about “ketofol” in different practice settings. Fourth, we had missing data fields in 22 pre-education surveys, which precluded analysis of responses to particular questions. Due to the anonymity of the survey, participants with incomplete surveys were unable to be contacted for completion. This limitation also led to inconsistency in some of the reported response numbers

Conclusions

The period prevalence of “ketofol” was greater for sedation than induction. A large percent of participants in the pre-education

survey reported barriers related to the admixture. The period prevalence following education showed a slight increase in both sedation and induction use, as well as a significant reduction in barriers following education. Oral presentations proved to be more effective than electronic presentations in reduction of the identified barriers. The decline in concerns related to the admixture and increasing prevalence revealed a positive educational impact. Period prevalence is trending up as a result of education, but allowing more time may show a significant practice change.

Lastly, exposure to alternative techniques requires substantial evidence for both safety and efficacy prior to a practice change. The current study demonstrates an increasing prevalence, although not significant, in the use of the admixture, resulting from increased exposure and administration that may eventually result in a practice change. The authors believe that, more importantly, it is of utmost importance to reflect our own practice and continuously ask ourselves whether we are providing the best care for the patient rather than reverting to what we are comfortable with.

Disclosures

All authors declare no conflicts of interest and/or financial disclosures.

Appendix 1: Survey

- In the last 5 years, have you used a combination of ketamine and propofol at the same time?
 - Yes (go to 2)
 - No (go to I. B)
 - B. What is the main reason you have not administered ketamine and propofol at the same time? (mark only one)
 - Lack of knowledge of acceptability of this combination
 - Lack of experience with this combination
 - Too time consuming to prepare
 - Satisfied with current practice of administering only one
 - Other (please specify) _____
(Proceed to question 8)
- Which of the following best describes the typical scenario in which you have used this combination of ketamine and propofol?
 - You recommended/ordered the combination
 - Someone else recommended/ordered the combination and you followed through with the administration
- How do you prefer to administer a combination of ketamine and propofol at the same time?
 - Mix them in the same syringe
 - Administer one right after the other with separate syringes
 - Other (please specify) _____
- What is the preferred dosage of ketamine and preferred dosage of propofol that you administer? Please specify: _____
- Have you used the combination of ketamine and propofol as an induction agent?
 - Yes (go to 6)
 - No (go to 7)
- Rate the typical level of hemodynamic stability with the combination of ketamine and propofol when used as an induction agent. Very stable, stable, unstable, very unstable

7. Select the primary reason you have not used the combination as an induction agent
- Lack of knowledge
 - Lack of experience with this combination
 - Too time consuming to prepare
 - Satisfied with current practice of administering only one
 - Other (please specify) _____

Ask everyone

8. Do you have concerns with the use of the combination of ketamine and propofol? Mark all that apply:
- No concerns
 - Concerns about compatibility of the two drugs
 - Uncertain about the benefit to using the two drugs together
 - The combination is not approved by FDA
 - The combination is not approved by my department/institution
 - I am unsure of how to properly dispose of mixed controlled substances
 - Other (please specify) _____

9. Have you had any previous education on current knowledge or practice of the combination of ketamine and propofol.

Yes/No

10. If a seminar or educational session regarding current knowledge and practice of the combination of ketamine and propofol was offered, how likely would you be to attend?

Not at all likely, somewhat likely, very likely

* Question 10 not included in post-survey

11. Select your appropriate title. Anesthesiologist, CRNA, SRNA, Resident
12. How many years have you been practicing anesthesia? 0–5 years, 5–10 years, 10–20 years, 20+ years

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