RESEARCH ARTICLE

Complications of Deep Sedation for Individual Procedures (Lumbar Puncture Alone) Versus Combined Procedures (Lumbar Puncture and Bone Marrow Aspirate) in Pediatric Oncology Patients

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ABSTRACT

BACKGROUND AND OBJECTIVES: Pediatric oncology patients frequently undergo procedural sedation. The goal of this study was to determine the safety of combining procedures into a single sedation encounter and to assess if the magnitude of any complication is significant enough to justify separate sedation encounters for multiple procedures.

METHODS: This retrospective review included pediatric oncology patients sedated for lumbar puncture alone or combined procedures (lumbar puncture and bone marrow aspirate) from January 2012 to January 2014. Demographic characteristics, medication dosing, procedural success, sedation duration, and adverse events (AEs) with associated required interventions were recorded. Sedation-related complications were separated into serious adverse events (SAEs) and AEs. Data were analyzed by using multivariable modeling.

RESULTS: Data from 972 sedation encounters involving 96 patients, each having 1 to 28 encounters (mean ± SD, 10 ± 5), were reviewed. Ninety percent were individual procedures and 10% were combined procedures. Overall, there were few SAEs, and airway obstruction was the most common SAE. Combined procedures required 0.31 mg/kg more propofol ($P < .001$) and took 1.4 times longer ($P < .001$) than individual procedures. In addition, when adjusting for possible confounding factors, the odds of having an SAE were 4.8 (95% confidence interval, 1.37–16.65); $P = .014$) times higher for combined procedures. All SAEs and AEs were manageable by the sedation team.

CONCLUSIONS: Combining procedures was associated with higher propofol doses, prolonged duration, and a small increase in likelihood of SAEs compared with individual procedures. All AEs fell within the scope of management by the sedation team. Balancing the increased, but manageable, risks versus the advantages of family/patient convenience, enhanced resource utilization, and minimization of potential neurotoxicity from anesthetics supports combining procedures when possible.

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Procedural sedation outside of the operating room is annually becoming more common and is now the standard of care for completion of many invasive diagnostic and therapeutic pediatric procedures.[1,2] Pediatric oncology patients undergo frequent invasive procedures, including lumbar punctures (LPs) and bone marrow aspirates (BMAs) or biopsies, for diagnostic and therapeutic purposes. These procedures require sedation to prevent excessive movement, to maximize success and accuracy of procedures, and for pain control.[3]

In general, children are at a greater risk for sedation-related adverse events (AEs) than adults, especially children with underlying conditions, such as leukemia and other oncologic diseases.[4,5] Little is known about the complication rates for performing these procedures individually (LP alone) versus combining (LP and BMA) them into a single sedation encounter. Sedation safety and success are maximized when evidence-based protocols are in place for uniformity of care, but no such standardized practices exist for sedation encounters in pediatric oncology patients.[6,7]

The objective of the present study was to quantify the complication rates for patients undergoing a single procedure versus combined procedures. We hypothesized that when both procedures are performed in a single sedation encounter, a higher rate of complications would occur due to higher drug doses, longer duration of sedation, and the need for additional medications. However, the magnitude of these complications must also be assessed to determine if they are significant enough to justify multiple sedation encounters.

METHODS

Study Design and Data Collection

This study was a retrospective chart review, approved by our institutional review board, of pediatric oncology patients who were sedated for LP alone or combined procedures (LP and BMA) at Children's Healthcare of Atlanta at Egleston from January 2012 to January 2014. This institution is a quaternary care, free-standing children's hospital in Atlanta, Georgia, at which ~3500 pediatric sedations are performed per year. This total includes both inpatient and outpatient procedures. For sedation encounters in oncology patients, the sedation itself was performed by physicians trained in pediatric critical care medicine or pediatric emergency medicine in accordance with American Academy of Pediatrics Guidelines for Sedation while a pediatric oncology physician or nurse practitioner performed the procedure(s).[8,9] The protocols used by the Children's Sedation Services at our institution have been published previously.[10] Usually, topical anesthetic (2.5% lidocaine with 2.5% prilocaine) is applied to the procedure site 30 to 45 minutes before the LP and/or BMA. Typically, LPs are performed by using a single medication. Propofol is the preferred drug at our institution; it is administered as an initial intravenous (IV) bolus dose of 3 mg/kg for induction and titrated by the sedation physician as-needed for the duration of the procedure. For combined procedures (LP and BMA), most sedation physicians administer a single IV bolus dose of fentanyl 1 μg/kg for analgesia followed by a propofol IV bolus dose of 3 mg/kg with subsequent titration or further bolus doses to effect.

Data were abstracted from the sedation and procedural notes within the electronic medical record. Our sedation team keeps a list of all patients (both inpatient and outpatient) who are sedated for procedures and imaging. This list was used to identify the pediatric oncology patients undergoing LP and/or BMA. Patient demographic characteristics, American Society of Anesthesiologists (ASA) classification, medication dosing, sedation and procedural success, sedation duration, potential risks for sedation-related complications, and sedation-related AEs with associated required interventions were collected.

Outcome and AE Measures

Successful completion of a procedure was based on the ability to obtain spinal fluid or BMA specimens. Sedation-related complications were separated into serious adverse events (SAEs) and AEs based on definitions from the Pediatric Sedation Research Consortium.[11] For the present article, SAEs were defined as any 1 of the following events: (1) emergent airway intervention; (2) airway obstruction; (3) aspiration; (4) cardiac arrest; (5) death; (6) laryngospasm; or (7) unplanned admission for outpatient procedures or an increase in the patient's level of care (transfer to ICU or prolonged recovery/monitoring). These SAEs are readily identifiable in the sedation notes. Emergent airway interventions included intubation or placement of an airway adjunct due to prolonged apnea or desaturation. Airway obstruction was defined as lack of air movement despite respiratory effort. Aspiration included suspected or witnessed tracheal aspiration of gastric contents associated with a worsened respiratory status compared with presedation status. Laryngospasm was defined as complete or near-complete lack of air movement with respiratory effort and/or stridor that was not relieved by repositioning or other noninvasive maneuvers. Unplanned admission and increase in level of care were combined into 1 variable. AEs were defined as any 1 of the following: agitation, apnea, coughing, desaturation, increased secretions, myoclonus, stridor, vomiting, wheezing, or unexpected change in heart rate or blood pressure >30% from baseline.

Data were abstracted from the electronic medical records by the study team and compiled into an Excel worksheet (Microsoft Corporation, Redmond, Washington) with dichotomous responses (yes or no) for each complication type and interventions required. In some cases, multiple complications occurred in a single patient encounter; each event was then counted separately to maximize their capture. Many patients were sedated more than once within the study time frame and appear in the data set multiple times. However, each sedation procedure was a unique event and is influenced by various patient, procedural, and sedation factors. Therefore, each sedation encounter was treated as the unit of observation.

Data were also collected on known risk factors for sedation-related complications such as upper respiratory tract infection (URTI), history of obstructive sleep apnea (OSA)/snoring, ASA class III or higher, and age.[12] Other potential risk factors present in the data included history of cerebral palsy,

reflux, pulmonary hypertension, cardiac disease, history of asthma/wheezing, prematurity, and trisomy 21. Height was not documented for all patients, and thus BMI could not be gathered as a measure of obesity. However, morbidly obese patients are excluded from sedation by the sedation team/protocol based on the patient's BMI and z score; z scores indicate how many SDs the BMI is from the mean for age. Patients with a z score >2.5 are required to have procedures performed with general anesthesia in the operating room.

Statistical Methods

Statistical analysis was performed by using SAS version 9.3 (SAS Institute, Inc, Cary, North Carolina). Statistical significance was assessed at the 0.05 level unless otherwise noted. For the purposes of statistical analyses, each sedation procedure was considered a unique event and used as the unit of analysis (as explained earlier). Demographic characteristics, stated sedation and procedure characteristics, and AEs were analyzed by using counts and frequencies, means and SDs, and medians and interquartile ranges, where appropriate. Patient and sedation characteristics were compared between procedure groups by using 2-sample t tests and χ^2 tests. When expected cell counts were small (<5), Fisher's exact test was used in place of the χ^2 test. Similarly, when continuous variables appeared non-normally distributed, a Mann-Whitney U test or 2-sample Kolmogorov-Smirnov test was used in place of the 2-sample t test. Generalized estimating equations (GEEs) were used to compare continuous outcomes (duration of sedation and propofol dose) between the 2 procedure groups while adjusting for sedation and patient-level covariates. GEEs were chosen to adjust for the clustering of sedations occurring within the same patient. SAE and AE rates were calculated and compared between sedation types by using similar methods.

RESULTS
Demographic and Sample Characteristics

We reviewed 972 sedation encounters in 96 different pediatric oncology patients who were sedated for individual (LP alone) or combined (LP and BMA) procedures between January 2012 and January 2014. Each individual patient had anywhere from 1 to 28 sedation encounters, with a mean ± SD of 10 ± 5 encounters per patient. An overwhelming majority of procedures were performed in patients with acute lymphoid leukemia (ALL) (88.6%), followed by lymphoma in 7.1% and acute myeloid leukemia in 4.3%. Tables 1 and 2 summarize our sample demographic characteristics and characteristics of the 972 sedation encounters. The median sedation time of the procedures was 11 minutes (range, 3–67 minutes). Ninety percent of sedations were for LP only ($n = 876$), and the remaining 10% were for combined procedures (LP and BMA) ($n = 96$). Procedural success was 99.9% for LPs ($n = 970$) and 100% for BMAs ($n = 96$). For LPs, 2.7% required >2 attempts; for BMAs, 1.5% took up to 3 attempts. Propofol was used in all sedation encounters unless the patient had a history of allergic reaction to propofol, in which case methohexital was used (1.2%). Fentanyl was added in 173 of the sedation encounters (17.8%) that included patients who were undergoing BMA ($n = 92$ [96% of combined procedures]) and patients who a difficult previous sedation encounter with propofol alone for LP ($n = 81$ [9.3% of LP-alone procedures]).

Comparison of Individual Versus Combined Procedures

Of the 972 sedation encounters, 90% were for LP alone and 10% were for LP and BMA. Table 2 compares sedation-related characteristics for the 2 procedure groups. Compared with sedation encounters performed for LP alone, patients undergoing combined procedures (LP and BMA) tended to have a higher median age (90 months vs 81 months; $P = .02$), weighed more (32 kg vs 23 kg; $P = .02$), and had a higher reported history of asthma/wheezing (15.6% vs 6.5%; $P = .001$).

The mean propofol dose used for the combined procedures was significantly higher than the mean dose used for an LP alone, as shown in Fig 1 (5.08 ± 2.60 mg/kg vs 4.77 ± 2.17 mg/kg; $P < .001$). After adjusting for weight, duration of sedation,

adjunctive use of fentanyl, and multiple sedation encounters in the same patient, the GEE model showed that higher doses of propofol were still observed for the combined procedures compared with LP alone ($P < .001$).

Similarly, the duration of sedation was significantly longer in combined sedation encounters compared with LP alone, as shown in Fig 2 (17 minutes vs 11 minutes; $P < .001$). After adjusting for the need for intervention, patient age, history of asthma/wheezing, use of fentanyl, and propofol dose, duration of the combined procedures was 1.4 times longer than for LP alone.

Among the 972 sedation procedures reviewed, there were 157 (16.2%) during which at least 1 unexpected sedation-related complication occurred, but some sedation encounters involved >1 event.

TABLE 1 Patient Demographic and Sedation Characteristics

	Sedation Encounters ($N = 972$) From 96 Patients
Patient gender	
Male	629 (64.7)
Female	343 (35.3)
Age, mo	
Median (IQR)	81.7 (50.5–154.1)
Minimum–maximum	10.8–276.3
Weight, kg	
Median (IQR)	23.6 (17.3 − 48.4)
Minimum–maximum	7.4–100.2
ASA class[a]	
II	79 (8.2)
III	881 (91.3)
IV	5 (0.5)
Procedure type	
LP	876 (90.1)
LP + BMA	96 (9.9)
Success rate	
LP ($n = 971$)[b]	970 (99.9)
BMA ($n = 96$)	96 (100.0)

Data are presented as n (%), unless otherwise indicated. IQR, interquartile range.
[a] Missing data ($n = 7$).
[b] Missing data ($n = 1$).

TABLE 2 Sedation Characteristics

Characteristics	LP Alone (n = 876)	LP +BMA (n = 96)	P
Demographic			
Male gender	566 (64.6)	63 (65.6)	.911
Age, median (IQR), mo	80.8 (50.9–150.3)	89.7 (47.4–164.0)	.023*
Weight, median (IQR), kg	22.7 (17.2–47.6)	32.3 (17.6–50.8)	.015*
ASA class[a]			
II	70 (8.1)	9 (9.5)	.717
III	795 (91.4)	86 (90.5)	
IV	5 (0.6)	0	
Risk factors for failed sedation			
URTI/cough	214 (24.4)	17 (17.7)	.142
OSA/snoring	49 (5.6)	6 (6.3)	.792
History of asthma/wheezing	57 (6.5)	15 (15.6)	.001*
Previous sedation reaction	10 (1.1)	3 (3.1)	.129
Sedation			
Primary sedative			
Propofol	865 (98.7)	95 (99.0)	1.00
Methohexital	11 (1.3)	1 (1.0)	
Adjunctive fentanyl	81 (9.3)	92 (95.8)	<.001*
Outcomes			
Duration of sedation, median (IQR), min	11 (9–14)	17 (13–22)	<.001*
AE	113 (12.9)	19 (19.8)	.061
SAE	31 (3.5)	7 (7.3)	.090
Intervention required	206 (23.5)	22 (22.9)	.900

Data are presented as n (%), unless otherwise indicated. IQR, interquartile range. *P < .05.
[a] Missing data (n = 7).

There were a total of 205 sedation-related events; 42 were defined as SAEs, and 163 were defined as AEs. Airway obstruction was the most commonly encountered SAE, with 30 events occurring during an LP alone (3.4%) and 7 during combined procedures (7.3%). There were also 2 laryngospasm events (2.1%); both events occurred during combined procedures, and 1 of these procedures had to be stopped because of the event. There were no aspirations, transfers to higher care, cardiac arrests, or deaths.

Of the SAEs, only 3 required emergent airway intervention. All 3 airway interventions were in different patients; 2 required laryngeal mask airways (LMAs), and a nasal trumpet and oral airway were placed in the third patient. One LMA was placed for airway obstruction and laryngospasm in an 18-month-old female patient with acute myeloid leukemia, ASA classification II, undergoing combined procedures; LP was successful on the first attempt, but the BMA required 3 attempts, and sedation duration was 27 minutes. The second LMA was placed for apnea during induction and desaturation despite continuous positive airway pressure (CPAP), jaw thrust, and positive pressure ventilation (PPV) in an 18-year-old male subject with ALL, ASA classification III, undergoing LP alone; the LP required 2 attempts, and the sedation duration was 16 minutes. A nasal trumpet and oral airway were placed for airway obstruction that did not improve with PPV in a 3-year-old girl with ALL, ASA classification III, who was undergoing LP alone; the procedure was successful on the first attempt, and sedation duration was 8 minutes. However, this patient had a history of trisomy 21, OSA/snoring, airway obstruction requiring CPAP in the multiple previous sedation encounters, and an
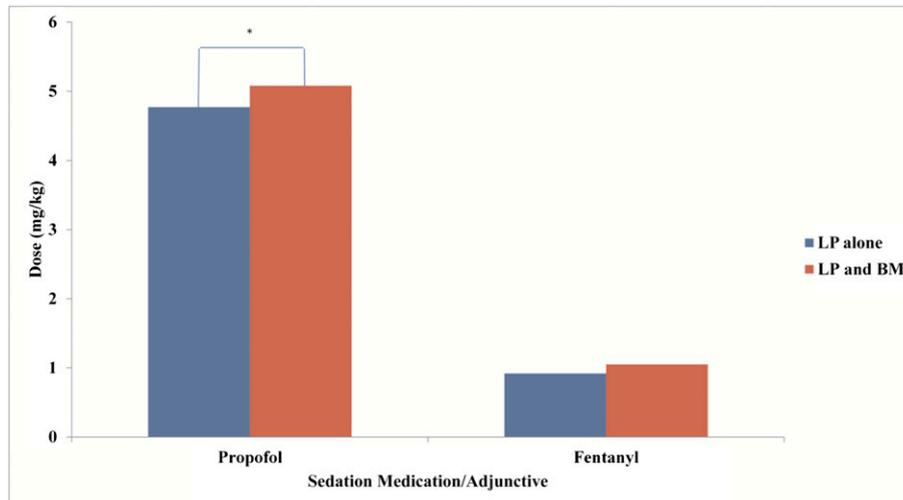
URTI/cough at the time of the sedation. In addition, 1 combined (LP and BMA) sedation procedure in a 3-year-old boy with ALL, ASA classification III, had to be stopped due to laryngospasm, airway obstruction, coughing, increased secretions and desaturation despite blow-by oxygen, jaw thrust, CPAP, suction, and PPV. Of note, all of these patients survived neurologically intact, with no apparent changes from baseline immediately after recovering from the sedation.

In univariate analysis, there was no statistically significant difference among the SAE rates in the LP-alone group versus the combined (LP and BMA) group (3.5% vs 7.3%). After adjusting for variables that differed between the 2 groups (including age, history of asthma/wheezing, adjunctive use of fentanyl, propofol dose, and clustering of sedations within a patient), the odds of having an SAE were 4.8 times higher when procedures were combined compared with when LP was performed alone (odds ratio [OR], 4.78 [95% confidence interval (CI), 1.38–16.57]; P = .014).

For AEs, desaturation (6.5%), apnea (3.6%), and unexpected change in heart rate or blood pressure (2.5%) were the most common. Most commonly required interventions were CPAP (9.5%), blow-by oxygen (7.8%), jaw thrust (5.3%), PPV (4.5%), and IV fluids (2.3%). There was no statistical difference in AEs between the LP-alone group and the combined procedures group (P = .61).

Risk Factors for Sedation-Related Events

Previously defined sedation risk factors were also analyzed to determine if they explained the differences in SAEs and AEs that were observed.[12] The most prevalent risk factors were URTI/cough (23.8%), history of asthma/wheezing (7.4%), and OSA/snoring (5.7%). The only risk factor that was significantly different between the patients undergoing individual and combined procedures was history of asthma/wheezing; 7% of patients undergoing LP alone had this history versus 16% of patients undergoing combined procedures (P = .001). Even after adjusting

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FIGURE 1 Dose of propofol and fentanyl used for individual versus combined procedures. *$P < .001$.

for this difference, the odds of SAE were still higher in the combined procedure group. In addition, the use of fentanyl was not a significant risk factor for SAEs in the multivariable risk factor model (OR, 2.3 [95% CI, 0.68–7.84]; $P = .179$). However, the use of fentanyl was a significant risk factor for AEs in the multivariable risk factor model (OR, 1.87 [95% CI, 1.09–3.19]; $P = .022$). All other risk factors were evenly distributed between the individual and combined procedure groups.

DISCUSSION

Procedural sedation by trained sedation providers outside of the operating room is rapidly becoming the standard of care at many institutions.[11–13] This use of deep procedural sedation has been shown to be safe when practiced by highly trained physicians who can quickly recognize and treat AEs.[14,15]

Pediatric patients with hematologic malignancies may need, on average, 20 painful procedures during their treatment course. These patients are at a reportedly higher risk for sedation-related events.[4,5] No evidence-based protocols or exact drug regimens exist for procedures in such patients. The goal of procedural sedation in these patients is to reduce anxiety, discomfort, and pain while providing optimal conditions for the procedure with minimal AEs.[16] Furthermore, combination of procedures such as LP and

BMA in 1 visit would greatly improve family satisfaction, optimize resource utilization, and is often dictated by the oncologic treatment protocols. The aim of the present study was to quantify the complication rates of combining procedures (LPs and BMAs) into a single sedation encounter versus performing them individually and to assess if the magnitude of these complications is significant enough to justify multiple sedation encounters.

We found that the combination of fentanyl and propofol when used for combined procedures (LP and BMA) during a single sedation encounter was associated with higher propofol doses; it prolonged the duration of sedation and increased the overall odds of having an SAE by 4.8 times. However, skilled sedation physicians quickly and easily managed these potential SAEs with basic interventions, and the immediate postsedation outcomes of these children were unaffected, with all patients returning to baseline state. Our sedation team is composed of either pediatric critical care medicine or pediatric emergency medicine physicians who are highly skilled in early recognition and management of airway issues in pediatric patients. They are also at the bedside throughout the sedation. Although the overall sedation and procedural success rates for combined procedures (LPs and BMAs) are high, the sedation provider needs to have adequate training and skills to recognize and treat

airway complications that can manifest during these sedation encounters. The exact reason for the higher incidence of SAEs, such as airway obstruction, in patients being sedated for combined procedures (LPs and BMAs) in our study is unknown. However, these are high-risk patients with underlying cancer and other comorbidities as evidenced by ASA classifications typically in the ASA III to IV range. Also, BMA is a much more painful procedure than LP, and this factor may play a role in our findings. In addition, it is noteworthy that overall, there were few SAEs in the study, and only a small group of the patients underwent combined procedures. Therefore, although there is an increased OR, it is important to note the wide CI that resulted from the small sample size, indicating that the possible association is still unclear and needs to be further studied.

Propofol is widely used for pediatric procedural sedation due to its unique pharmacologic features such as rapid and predictable onset, short duration of action, and rapid recovery.[17] The synergy of propofol and an opioid, such as fentanyl, has been well described in the anesthesia literature.[18] One pediatric study has shown that the combination of fentanyl and propofol for LP in pediatric patients with acute hematologic malignancies resulted in lower propofol doses and fewer AEs.[19] Furthermore, fentanyl is used in almost all combined procedures but only in one-tenth
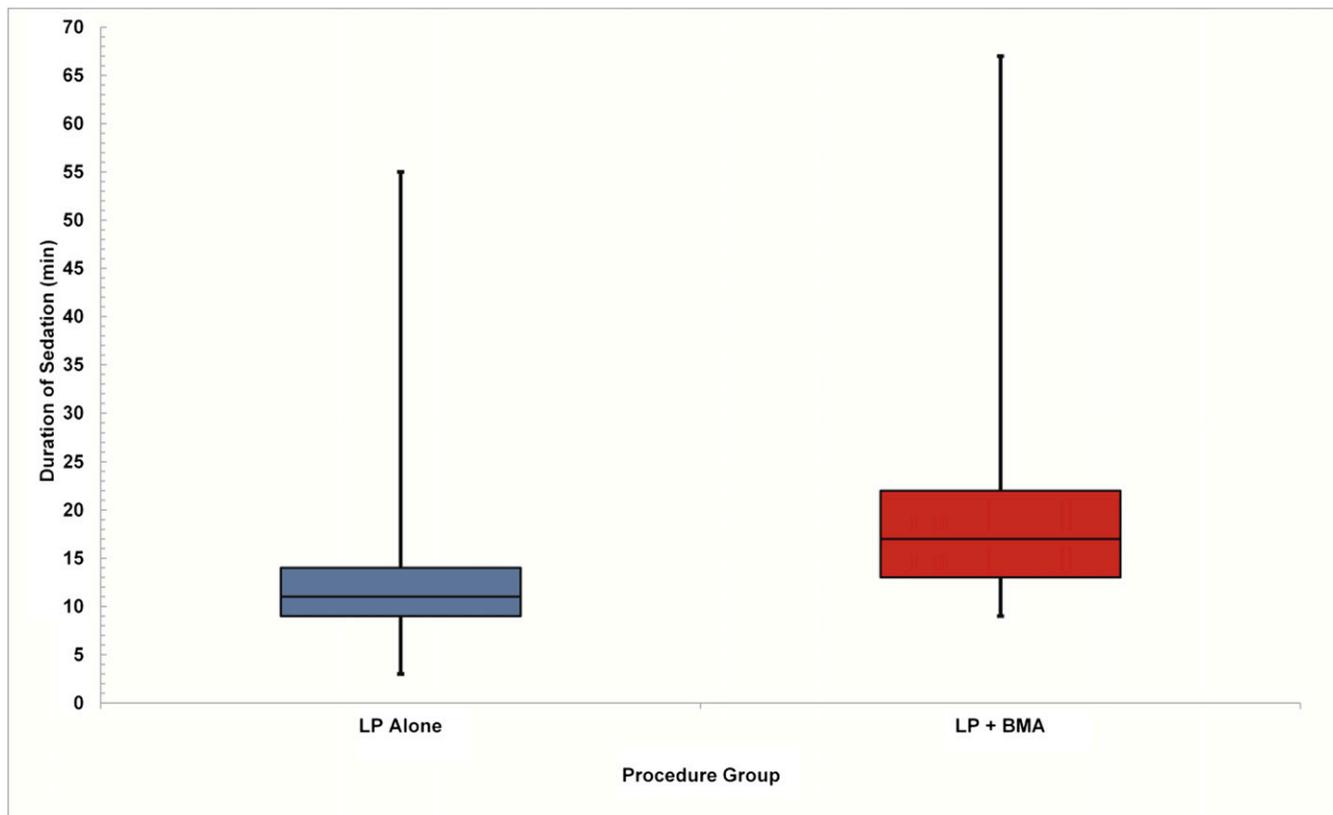
FIGURE 2 Duration of sedation for individual versus combined procedures.

of the individual procedures. Although the OR (2.3) to adjust for use of fentanyl was not statistically significant, it may be clinically significant. Therefore, we cannot conclude with certainty that use of fentanyl did not contribute somewhat to the increased risk of SAE.

Another important concept to consider is the newly developing concern for neurotoxicity from repeated use of propofol.[20] In recent animal studies, propofol has been shown to cause apoptosis of neurons and oligodendrocytes in monkeys. Based on our sedation model, a majority of the propofol used in procedural sedation is given as an initial bolus. Therefore, combining procedures may decrease lifetime propofol exposure and may in turn decrease possible neurotoxicity in these at-risk patients.

Overall, based on our findings and in combination with the literature, we believe that procedures should be combined whenever possible for family/patient

convenience (fewer missed work/school days and less anxiety), to maximize resource utilization and to minimize propofol exposure, and because the relatively few SAEs that occurred were easily managed by experienced providers. In addition, none of the SAEs that occurred required admission or led to escalation of care, cardiac arrest, or death. However, this decision to perform procedures individually versus combining them was ultimately dictated by the pediatric oncology treatment protocols for most of these patients.

Limitations of the present study include its retrospective nature, single-center experience, and use of a nonstandardized database with some variables that were challenging to objectify. The incidence of AEs may have been underestimated because the data were obtained via chart review. Furthermore, when we collected data for this study, the use of end-tidal monitoring was not mandatory at our institution, and this factor may have resulted in a significantly lower capture rate of brief

apnea events immediately after induction with propofol.

In addition, there are no universally accepted definitions for SAE versus AE; however, as a foundation, we used a predetermined independent standard defined by the Pediatric Sedation Research Consortium.[11] In previous consortium data, SAEs have been defined as death, cardiac arrest, emergency anesthesia consultation, aspiration, unplanned admission, or increases in level of care. We elected to also include airway obstruction, laryngospasm, and nonanesthesia airway intervention in this category for our study because in pediatrics, even minor airway compromise due to incomplete obstruction or laryngospasm can be the inciting event that quickly leads to respiratory failure or cardiac arrest.[21,22] Airway obstruction was the most common AE in our study, but it was difficult, due to the retrospective nature of the study, to objectively differentiate obstruction that required minor airway interventions versus more serious airway

interventions. Pediatric patients are at a higher risk for dynamic airway collapse in the presence of acute airway obstruction due to smaller airway size, less developed cartilaginous support, and increased compliance of airway structures.[23] In addition, laryngospasm is frequently associated with the medications used for pediatric sedation and often requires airway intervention.[15,24] Therefore, rapid recognition of both airway obstruction and laryngospasm during procedural sedation with appropriate airway intervention directly prevents further deterioration and more serious sedation-related events.[25]

CONCLUSIONS

In this cohort of pediatric oncology patients undergoing LP alone or LP and BMA for diagnostic and therapeutic purposes, combining procedures into a single sedation encounter was associated with higher drug doses, longer duration of sedation, and a higher incidence of SAEs. However, in the hands of advanced, trained sedation providers, combining procedures (LP and BMA) was highly successful, with an overall low incidence of complications and no poor immediate postsedation outcomes. All potential events, both AEs and SAEs, were well within the scope of management by the highly trained sedation team. Assessing the magnitude of these complications is critical in determining risk/benefit approaches toward sedation strategies. Balancing increased but manageable risks versus the advantages of family/patient convenience, enhanced resource utilization, and minimization of potential lifelong neurotoxicity from anesthetics supports combining procedures when possible in similar clinical settings. However, providers should continue to maintain a heightened sense of awareness and vigilance throughout the procedure.

Although the oncologic treatment algorithms dictate many of the procedures in pediatric oncology, similar future studies with nononcologic patients would be able to provide general pediatric health care providers and families with the data to make informed decisions about combining procedures versus performing them separately for more general pediatric

patients. Although the specific procedures (LP and BMA) we studied may not be commonly required in general pediatric patients, these findings can be applied to many other procedures and opens the door for future studies, such as combining imaging studies and/or multiple noninvasive or less invasive procedures.

Acknowledgments

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