Randomized Clinical Trial Comparing Procedural Amnesia and Respiratory Depression Between Moderate and Deep Sedation With Propofol in the Emergency Department

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ABSTRACT

Objectives: The objective was to determine if there is a difference in procedural amnesia and adverse respiratory events (AREs) between the target sedation levels of moderate (MS) and deep (DS) procedural sedation.

Methods: This was a prospective, randomized clinical trial of consenting adult patients planning to undergo DS with propofol between March 5, 2015, and May 24, 2017. Patients were randomized to a target sedation level of MS or DS using the American Society of Anesthesiologist's definitions. Drug doses, vital signs, observer's assessment of alertness/sedation (OAAS) score, end-tidal CO_2 ($ETCO_2$), and the need for supportive airway maneuvers (SAMs; bag-valve mask use, repositioning, and stimulation to induce respirations) were monitored continuously. A standardized image was shown every 30 seconds starting 3 minutes before the procedure continuing until the patient had returned to baseline after the procedure. Recall and recognition of images were assessed 10 minutes after the sedation. Subclinical respiratory depression (RD) was defined as $SaO_2 \leq 91\%$, change in $ETCO_2 \geq 10$ mm Hg, or absent $ETCO_2$ at any time. The occurrence of RD with a SAM was defined as an ARE. Patient satisfaction, pain, and perceived recollection and physician assessment of procedure difficulty were collected using visual analog scales (VASs). Data were analyzed with descriptive statistics and Wilcoxon rank-sum test.

Results: A total of 107 patients were enrolled: 54 randomized to target MS and 53 to DS. Of the patients randomized to target MS, 50% achieved MS and 50% achieved DS. In the target DS group, 77% achieved DS and 23% achieved MS. The median total propofol dose (mg/kg) was lower in the MS group: MS 1.4 (95% confidence interval [CI] = 1.3–1.6, IQR = 1) versus DS 1.8 (95% CI = 1.6–2.0, IQR = 0.9). There were no differences in median OAAS during the procedure (MS 2.4 and DS 2.8), lowest OAAS (MS 2 and DS 2), percentage of images recalled (MS 4.7% vs. DS 3.8%, p = 0.73), or percentage of images recognized (MS 61.1% vs. DS 55%, p = 0.52). In the MS group, 41% patients had any AREs compared to 42% in the DS group (p = 0.77, 95% CI difference = –0.12 to 0.24). The total number of AREs was 23% lower in the MS group (p = 0.01, 95% CI = –0.41 to –0.04). There was no difference in patient-reported pain, satisfaction, or recollection VAS scores. Provider's rating of procedural difficulty and procedural success were similar in both groups.

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Conclusions: Targeting MS or DS did not reliably result in the intended sedation level. Targeting MS, however, resulted in a lower rate of total AREs and fewer patients had multiple AREs with no difference in procedural recall. As seen in previous reports, patients who achieved MS had less AREs than those who achieved DS. Our study suggests that a target of MS provides adequate amnesia with less need for supportive airway interventions than a target level of DS, despite the fact that it often does not result in intended sedation level.

Deep procedural sedation (PS) with propofol for painful procedures in the emergency department (ED) is well described.[1] Its use for MS has also been described.[1,2] The American Society of Anesthesiologists (ASA) defines MS as the ability to purposefully respond to a tactile or verbal stimuli throughout the sedation, and deep sedation (DS) as responding to painful stimuli.[3] Serious adverse events from propofol are well described but rare.[4] The more frequently occurring minor adverse events of subclinical respiratory depression (RD) and supportive airway maneuvers (SAM) are often used in research to compare agents and protocols, with the assumption that their occurrence is sometimes associated with serious adverse events.[5,6] Deeper levels of sedation have been associated with more frequent cardiorespiratory adverse events, but are typically associated with less recall and improved procedural facilitation.[7–9] Lighter levels of sedation could lead to inadequate amnesia during portions of the procedure. A safe sedation goal is to choose the lightest level of sedation that leads to procedural amnesia and allows the procedure to be completed effectively without causing adverse cardiorespiratory effects.[1]

Prior studies of memory formation during PS have utilized visual analog scale (VAS) scores of the patients' perceived procedural recall and verbal prompt recall.[2,10] However, it has been noted that patients tend to have more precise measures of recall with pictures compared to words.[11] Visual memory prompts also allow for the use of a multiple-choice recognition test after sedation; thus with use of this method, evidence of memory formation can more accurately and precisely be detected than by using free recall alone.[12] A visual prompt memory assessment consisting of a set of standardized images was developed prior to this study and tested against a previously used verbal prompt memory assessment. When patients were given both verbal and visual prompts prior to sedation, patients could recall 59% more visual prompts than verbal prompts and recognized 98% of the images presented to them.[12] Because of these findings, the visual memory test was used in this study to detect amnesia during sedation.

These sedation levels of moderate and deep were developed as crude measures of the risk of ventilatory compromise, based on the fact that ventilatory changes appeared to be more common when DS was achieved than when MS was achieved. Although the achievement of MS and DS are common in the ED and their safety are well described, the differences in the safety and effectiveness of using these two sedation level goals as predetermined target sedation levels, and their effect on the outcome of sedation procedures has not been extensively compared.

The objective of this study was to determine whether assigning a target sedation level of MS or DS resulted in a difference in procedural amnesia and adverse respiratory events (AREs) between the sedation targets of MS and DS. Our hypothesis is that targeting MS would lead to a 25% decrease in AREs without affecting procedural amnesia. secondary outcomes included the achieved sedation level; differences in the need for SAMs; the dosage of propofol used to achieve the sedation target; the provider's perceived procedural difficulty; and patient's perception of pain, recall, and satisfaction with the procedure.

METHODS

Study Design

This was a prospective, randomized clinical trial of adults ED patients undergoing PS using propofol. Patients were enrolled between March 5, 2015, and May 24, 2017. Patients were randomized to have the treating physician target a level of MS or DS. The hospital's institutional review board approved the study, and all patients provided written informed consent. This trial was registered with ClinicalTrials.gov (NCT00997321).

Study Setting and Population

The study was performed in the ED at an urban county hospital with approximately 110,000 annual ED visits. Patients were eligible for enrollment if they were ≥18 years of age, were to undergo DS for any reason using propofol, and had an ASA physical status level of 1 or 2.[13] Patients were excluded from

enrollment if they were unable to give informed consent in English, pregnant, incarcerated, or clinically intoxicated. Eligible patients were approached by a trained research associate (RA), who were present in the ED 24 hours per day. Prior to enrollment, patients provided written informed consent.

Study Protocol

Patients experiencing pain prior to the PS were treated with intravenous (IV) morphine (0.1 mg/kg IV followed by 0.05 mg/kg IV every 10 minutes as needed/tolerated for pain relief) as soon as possible in their treatment and at least 20 minutes prior to their sedation procedure. Patients were placed on cardiac, blood pressure, pulse oximeter, and nasal end-tidal CO_2 ($ETCO_2$) monitors. The $ETCO_2$ monitor (Capnocheck Plus, Smiths Medical BCI) displays a numerical value continuously with a waveform. Supplemental facemask oxygen was applied according to standard protocol for PS in the ED.

The randomization order was determined by a computer-generated random number. Sequentially numbered sealed envelopes contained the group assignment. After enrollment, an RA opened the next envelope and disclosed the randomization allocation to the physician, which instructed them to target the sedation level to moderate or deep. The patient was blinded to the sedation target level. Two physicians were present for each enrollment, one to complete the procedure and one to perform the sedation. The dosage of propofol used to achieve the assigned target sedation level was at the discretion of the sedating physician.

Outcome Measures

Before the start of the procedure, baseline vital signs were recorded. Heart rate, pulse oximetry, blood pressure, and $ETCO_2$ were monitored continuously starting 3 minutes prior to the procedure and continuing until the patient had regained their baseline mental status after the procedure. The lowest value was recorded every 30 seconds. We continuously monitored for any SAMs, which were defined as any use of airway adjuncts such as a bag-valve mask apparatus, airway repositioning such as a jaw thrust, the use of an oral airway or nasal trumpet to improve ventilation, and any stimulation to induce respirations such as a sternal rub or glabellar tap.[14] The observer's assessment of alertness/sedation (OAAS) score was recorded every 30 seconds (Figure 1). The occurrence of any SAM and any loss of the $ETCO_2$ waveform (evidence of airway obstruction or apnea) was recorded.[9,13–18]

Responsiveness	Score
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1

Figure 1. Observer's assessment of alertness/sedation score.

Beginning 3 minutes prior to the procedure, RAs presented visual prompts every 30 seconds from a standardized visual memory assessment tool and asked the patient to verbally state what the visual prompt represented. The patient's ability to describe the visual prompt were recorded after each presentation. RAs showed visual prompts until the patient returned to their baseline mental status after the procedure. If the patient's eyes were closed when the image was presented, the RAs called the patient's name several times to attempt to have the patient open his or her eyes and recorded whether the patient opened their eyes to look at the prompt. Ten minutes after their return to baseline mental status, patients were given 2 minutes to state all remembered visual prompts, and then a multiple-choice image recognition test was completed. Each question on the multiple-choice test included a visual prompt that was presented to the patient alongside two other similar black and white images not shown to the patient.

After the procedure, the physician completed a standardized data collection sheet to describe any complications encountered, including, but not limited to increased supplemental oxygen, aspiration, transfer to higher level of care after procedure, arrhythmias, hypotension (<90 mm Hg or decrease of >20% from baseline), bag-mask ventilation use, and loss of protective airway reflexes. Physicians were also asked to report whether the achieved level of sedation was moderate or deep. Physician assessment of procedure difficulty and patient satisfaction, pain, and perceived patient recollection were collected using 100-mm VAS.

We calculated the procedure duration, the recovery time (from procedure completion until return to baseline mental status), sedation duration, total amount of propofol given, lowest OAAS score, mean OAAS score during the procedure, and highest and lowest vital sign measurements. Research assistants also recorded any prompts that patients were able to recall and recorded the patients' answers to the multiple-choice recognition test. The onset of amnesia was defined as when patients stopped answering questions correctly on the multiple-choice quiz or the last image freely recalled prior to propofol, whichever was closer to the dose of propofol. The end of the amnestic period was defined as the next time a patient was able to correctly answer three sequential multiple-choice questions or was able to freely recall an image after the initial propofol dose.

Our primary outcome was the proportion of patients that experienced AREs. AREs were defined as the occurrence of one or more clinical features of RD combined with one or more associated SAMs.[5] Clinical features of RD included an oxygen saturation of ≤91%, a change from baseline $ETCO_2$ of ≥10 mm Hg, or a loss of $ETCO_2$ waveform (either from central apnea or from upper airway obstruction). These criteria have been used in prior studies of PS to detect evidence of RD.[5,17,19–21]

Secondary outcomes included procedural amnesia; lowest OAAS during the procedure; incidence of retrograde amnesia; patient VAS scores for recall, pain, and satisfaction; procedure success; physician procedure difficulty VAS scores; and incidence of adverse outcomes (hypotension, arrhythmia, aspiration, etc.).

Data Analysis

Data were entered into Excel (Microsoft Corp.) for analysis. The data were analyzed with descriptive statistics when appropriate. The rate of image recall and recognition between the groups; the occurrence rate of AREs, SAMs, and RD; the rate that patients' achieved the target sedation depth; VAS scores; and the propofol dosage used were tested for equality with the Wilcoxon rank sum test. To detect a 25% difference in the proportion of patients experiencing an ARE (estimated to be 41% at baseline based on prior literature[5]), with an alpha of 0.05 and a beta of 0.2 (80% power), power analysis indicated that 50 patients per group were required.

RESULTS

We enrolled 116 patients of the 1103 screened patients (Figure 2). Forty-eight patients were eligible for the study but not approached for enrollment by a RA. Nine patients were excluded from data analysis (four patients did not undergo sedation after enrollment, one patient left the ED prior to the procedure, two patients withdrew from study, one patient was unable to see the visual prompts, and one protocol violation). The protocol violation occurred when a

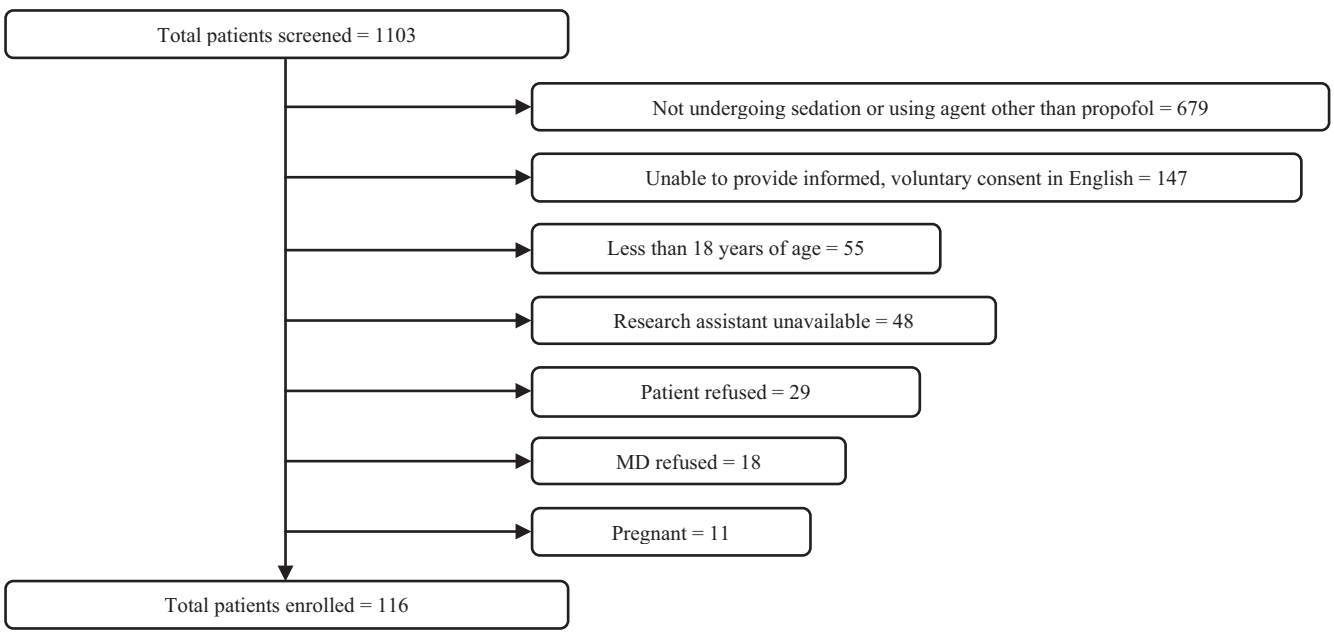

Figure 2. Screening and enrollment data. ARE = adverse respiratory event; DS = deep sedation group; MS = moderate sedation group.

research assistant enrolled the patient but was not available to collect data during the sedation. A total of 54 patients were randomized to a target of MS and 53 patients to a target of DS. No significant adverse events occurred (arrhythmias, intubation, aspiration, transfer to higher level of care).

The baseline characteristics, propofol dosing, and procedures performed are summarized in Table 1. The randomization groups did not differ significantly in size or in baseline characteristics. The median initial dose of propofol did not significantly differ between randomization groups ($p = 0.09$), but the median total dose of propofol used for the entire sedation did ($p = 0.03$).

Patient outcomes by randomization group are summarized in Table 2. In the MS group, 21 of 54 (41%) patients had an ARE compared to 24 of 53 (42%) in the DS group ($p = 0.77$). However, there were 23% more total AREs in the DS group ($p = 0.01$) and 17% more patients had more than one ARE during the sedation in the DS group ($p = 0.03$). All SAMs were associated with clinical evidence of RD. There was no difference in the dose of propofol given to those patients that had an ARE versus those that did not. The median propofol dosage for each randomization group and separated by the number of AREs is summarized in Figure 3. The individual propofol doses given for each patient in the study categorized by number of AREs is displayed in Figure 4.

A total of 71 SAMs were performed on patients. Eight patients required bag-mask ventilation: two of 54 in the MS group and six of 53 in the DS group ($p = 0.13$). One of these patients required manual ventilation for 7.5 minutes (propofol dose 2.8 mg/kg); the remainder required less than 60 seconds of bag-mask ventilation. The mean propofol dose for these patients was 1.1 mg/kg and the mean weight was 81 kg. A total of 32 patients required airway repositioning: 14 in the MS group compared to 18 in the DS group ($p = 0.37$). Physical stimulation occurred 31 times: 14 in the MS group and 17 in the DS group ($p = 0.47$).

Based on our established criteria for RD, 70% of patients in the MS group and 64% of patients in the DS group experienced RD. Of those patients, 40 of 73 (54%) had an isolated change in $ETCO_2 \geq 10$ without hypoxia or loss of waveform. Five patients (7%) had isolated hypoxia, six patients (8%) had hypoxia and change in $ETCO_2 \geq 10$, 24 patients (32%) had loss of $ETCO_2$ waveform without hypoxia, and two patients (3%) had loss of waveform and hypoxia. Of the patients who met criteria for RD, most had change in $ETCO_2 \geq 10$ except for four in the MS group (7%) and three in the DS group (6%). There was no difference the randomization groups in terms of RD or loss of $ETCO_2$ waveform between the randomization groups. No patient had an oxygen saturation < 92% for longer than 60 seconds.

Table 1
Baseline Characteristics by Randomization Group

Characteristic	MS ($n = 54$)	DS ($n = 53$)
Age (years)	41.5 (18–78, 27)	39 (20–73, 25)
Male sex (%)	45.3	52.8
Weight (kg)	90 (54–167, 24)	81.6 (49–127, 28)
Initial sBP (mm Hg)	136 (95–175, 37)	135 (94–182, 27)
Initial heart rate	83 (55–137, 19)	86.5 (53–140, 21)
Initial $ETCO_2$	40 (18–50, 6)	37 (20–48, 6)
Initial propofol dose (mg/kg)	0.96 (0.8–0.9, 0.5–1.5, 0.2)	0.99 (0.9–1.0, 0.5–1.7, 0.1)
Total number of doses given	2.5 (2.3–3.1, 1–9, 1)	3.0 (2.7–3.9, 1–11, 2)
Total propofol dose (mg/kg), p = 0.029	1.4 (1.4–1.7, 0.7–3.8, 1.0)	1.8 (1.7–2.2, 0.9–5.0, 0.9)
Abscess incision and drainage performed	18 (33)	18 (34)
Orthopedic reduction performed	30 (55)	33 (63)
Cardioversion performed	3 (6)	1 (2)
Other procedure performed (i.e., wound care, foreign body removal)	3 (6)	1 (2)
Image recall BP (median %)	39.5 (31.0–47.9, range 0–100, 32)	44.4 (34.5–54.3, range 0–100, 47)
Image test percentage correct BP	100 (94.9–100, 16.7–100, 6)	100 (94.1–100, 0–100, 2)

Data are reported as median (range, IQR), (95% CI, range, IQR), or median (% of total) unless otherwise specified. The difference between the randomization groups was not significant unless noted above.
BP = before propofol; DS = deep sedation; MS = moderate sedation; sBP = systolic blood pressure.

Table 2
Results Summarized by Randomization Group

Outcome	MS (n = 54)	DS (n = 53)	p-value, (difference in proportion, 95% CI)
Need for one airway intervention	21 (39)	24 (45)	0.94 (0.06, –0.11 to 0.24)
Need for > 1 airway intervention	6 (11)	15 (28)	0.025 (0.17, 0.02 to 0.32)
Total airway maneuvers	29	41	0.01 (0.24, 0.05 to 0.39)
Need to use bag-valve mask	2 (3.7)	6 (11.3)	0.13 (0.08, –0.03 to 0.19)
$ETCO_2$ waveform absence	12 (22)	14 (26)	0.71 (0.04, –0.12 to 0.20)
Hypoxia ($SaO_2 \leq 91\%$)	7 (13)	7 (13)	0.98 (0, –0.13 to 0.13)
Subclinical RD	38 (70)	34 (64)	0.57 (0.06, –0.11 to 0.23)
Decrease in sBP (%)	9.0 (7.8–13.2, 0–34, 16)	8.9 (7.4–13.2, 0–47, 13)	0.78
Hypotension (sBP < 90 or decrease of >20% from baseline)	11 (20)	7 (13.2)	0.52
OAAS nadir	2 (1.8–2.2, 1–4, 1)	2 (1.7–2.3, 1–4, 1)	0.96
OAAS mean during procedure	2.4 (2.1–2.7, 1–5, 1)	2.8 (2.4–3.1, 1–4.9, 1)	0.13
Achieved target sedation level	27 (50)	41 (77)	0.02 (0.25, 0.06 to 0.41)
Time to return to baseline (min)	13 (11.5–14.5, 4–30, 5)	12.5 (10.5–14.5, 6.5–39, 7)	0.87
Procedure successful	52 (96)	52 (98)	0.76 (0.04, –0.04 to 0.12
Duration of procedure (min)	6 (5.0–7.0, 0.5–17.5, 5.5)	7.5 (5.9–9.1, 0.5–34.5, 5.1)	0.07
Patient pain VAS score (cm)	0.02 (0.0–0.1)	0.02 (0.0–0.1)	0.48
Patient perceived recall VAS score (cm)	0.1 (0.0–0.2)	0.1 (0.0–0.2)	0.47
Patient satisfaction VAS score (cm)	0.02 (0.0–0.1)	0.03 (0.0–0.1)	0.72
Procedure difficulty VAS score (cm)	0.13 (0.1–0.2)	0.16 (0.1–0.2)	0.65

Data are reported as n (%), median (95% CI, range, IQR), or median (95% CI).
DS = deep sedation; $ETCO_2$ = end-tidal CO_2; MS = moderate sedation; OAAS = observer's assessment of alertness/sedation; RD = respiratory depression; sBP = systolic blood pressure; VAS = visual analog scale.

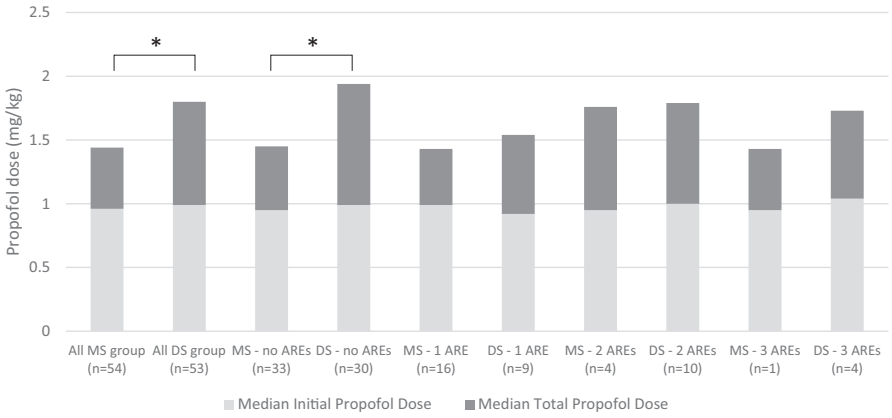

Figure 3. Median initial and total propofol dose by randomization group separated by number of AREs. (*p < 0.05). ARE = adverse respiratory event; DS = deep sedation group; MS = moderate sedation group.

All of the patients were successfully sedated to a moderate or deep level of sedation. Only 50% assigned to MS achieved the targeted sedation depth (remainder achieved DS) and 77% assigned to DS achieved DS with the remainder achieving MS (p = 0.02). There was no significant difference in patient pain, perceived recall, or satisfaction. Providers did not rate the procedure as more difficult and there was no difference in procedural success rate. Return to baseline mental status was 13 minutes (95% confidence interval [CI] = 11.5–14.5 minutes) for the MS group and 12.5 minutes (95% CI = 10.5–14.5 minutes) for the DS group.

Differences in image prompt recall and recognition are summarized in Table 3. Baseline memory as tested by preprocedural prompt recall and recognition did not differ between randomization groups (Table 1). All patients were able to recall at least one image

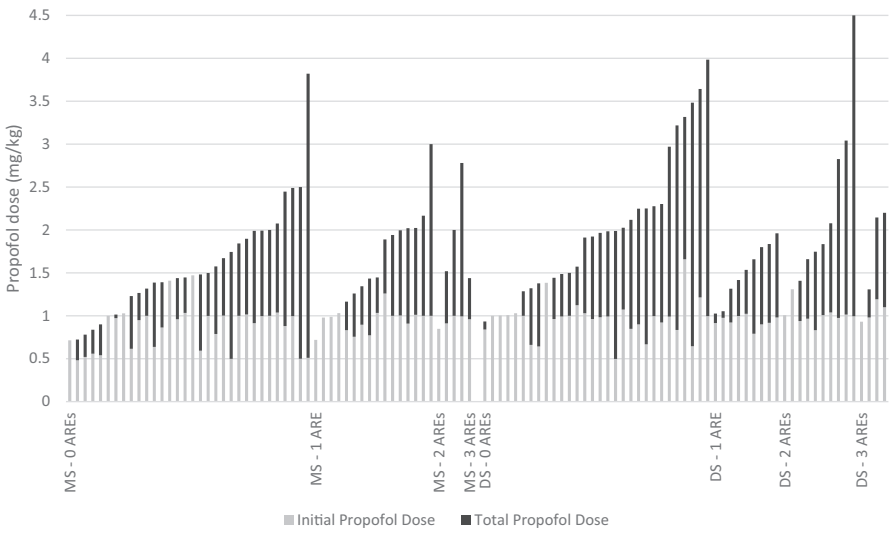

Figure 4. Individual patient initial and total propofol dose by randomization group and number of AREs. ARE = adverse respiratory event; DS = deep sedation group; MS = moderate sedation group.

presented to them prior to propofol administration. Thirty-two patients (30%) did not recall any images after propofol (MS group 15/54 [30%] and DS 17/53 [32%], p = 0.72). There were no significant differences between the MS and DS group in the ability of patients to recall or recognize images presented during the procedure or the duration of the sedation. The duration of amnesia using image recall and image recognition was calculated. After the last dose of propofol, patients did not recall an image for a median of 8.3 minutes in the MS group (95% CI = 7.2–9.3) and 6 minutes in the DS group (95% CI = 4.3–7.7). Amnesia resolution was detected sooner using the multiple-choice test compared free image recall (5.5 minutes vs. 7.2 minutes, p = 0.03). In total, 41 patients had some detectable memory formation during the procedure (18 in MS group and 23 in DS group). Of those who had recall or recognition of images during the procedure, 12% had higher recall VAS scores (p = 0.04), higher OAAS during the procedure (3 vs. 2.3, p < 0.001), and longer procedures (8.5 minutes vs. 6 minutes, p = 0.004) and were less likely to achieve DS (p = 0.01). Thirty-two patients had at least 1 minute of retrograde amnesia prior to the first dose of propofol. There was no difference in the randomization group, achieved sedation level, initial or total propofol dosage, number of propofol doses, patient weight, or procedure duration between those who did and did not have retrograde amnesia.

Respiratory depression, rate of AREs, and amnesia were compared by the achieved level of sedation in

Table 3
Procedural Amnesia Results

Result	MS (*n* = 54)	DS (*n* = 53)	p-value
Image recall sum (*n*)	6 (4.9 to 7.1, 4)	6 (4.2 to 7.8, 5)	0.91
Image recall AP (%)	4.7 (2.9 to 6.5, 8)	3.8 (1.0 to 6.6 8)	0.73
Time from last recall BP to propofol dose (min)	1 (0.4 to 1.6, 1.5)	0.5 (0.2 to 0.8, 1.5)	0.10
Time from first propofol dose to next recall (min)	9 (7.4 to 10.6, 4)	8 (5.8 to 10.2, 8)	0.18
Time from last propofol dose to next recall (min)	8.3 (7.2 to 9.3, 5)	6 (4.3 to 7.7, 9)	0.08
Image test correct AP (%)	55 (49.7 to 60.3, 21)	52.4 (46.7 to 58.0, 21)	0.92
Image test correct AP with eyes open (%)	61.1 (55.0 to 67.2, 32)	55 (48.5 to 61.5, 26)	0.52
Image test correct of described prompts AP (%)	64.7 (57.7 to 71.7, 38)	62.5 (55.7 to 69.3, 26)	0.81
Patients with recall of image during procedure	4 (8.9)	6 (15)	0.61
Patients with recognition of > 3 sequential images during the procedure	17 (33)	22 (40.7)	0.25
Time from last stretch of 3 correct answers and initial propofol dose (min)	0.0 (–0.3 to 0.3, 0)	0.0 (–0.1 to 0.1,0)	0.66
Time from last propofol to next stretch of 3 correct (min)	5.3 (4.7 to 7.1, 5.2)	5.0 (4.1 to 6.1, 4)	0.44

Data are reported as median (95% CI, IQR) or *n* (%)
AP = after propofol; BP = before propofol; DS = deep sedation; MS = moderate sedation.

Table 4
Results Summarized by Achieved Sedation Level

Result	MS (n = 39)	DS (n = 68)	p-value (difference in proportion, 95% CI)
Initial propofol dose (mg/kg)	0.99 (0.9–1.1)	0.98 (0.9–1.0)	0.92
Total number of propofol doses	3 (2.4–3.6)	3 (2.5–3. 5)	0.73
Total propofol dose (mg/kg)	1.5 (1.3–1.7)	1.5 (1.3–1.7)	0.69
OAAS during procedure	3.0 (2.7–3.3)	2.3 (2.1–2.5)	0.001
RD	21 (54)	53 (78)	0.04 (0.24, 0.06 to 0.41)
$ETCO_2$ waveform absence	6 (15)	20 (29)	0.18 (0.14, –0.03 to 0.28)
Occurrence of one ARE	5 (13)	39 (57)	0.001 (0.45, 0.26 to 0.57)
Occurrence of > 1 ARE	1 (3)	20 (29)	0.02 (0.27, 0.13 to 0.39)
Need to use bag-valve mask	0 (0)	8 (12)	0.03 (0.12, 0.01 to 0.22)
Total AREs	6	64	0.001 (0.79, 0.62 to 0.88)
Image recall AP (%)	5.2 (2.2–8.2)	3.4 (1.4–5.4)	0.27
Image test percentage correct AP	60.0 (52.8–67.2)	49.3 (45.3–53.2)	0.003
Image test percentage correct AP eyes open	65.0 (56.5–73.4)	53.2 (48.4–58.0)	0.01
Patients with recall of image during procedure	6 (15.4)	4 (5.8)	0.40 (0.10, –0.02 to 0.24)
Patients with recognition of > 3 sequential images during the procedure	21 (53.8)	18 (26.5)	0.02 (0.27, 0.08 to 0.45)
Patient pain VAS score (cm)	0.05 (0.0–0.1)	0.01 (0.0–0.1)	0.22
Patient perceived recall VAS score (cm)	0.13 (0.0–0.2)	0.08 (0.0–0.1)	0.08

Data are reported as median (95% CI) or n (%)
AP = after propofol; ARE = adverse respiratory event; DS = deep sedation; MS = moderate sedation; OAAS = observer's assessment of alertness/sedation; RD = respiratory depression.

Table 4. There was no difference in the total dosage of propofol used or the number or propofol doses between those that achieved MS and DS. Those who achieved MS had a 24% decrease in the incidence of RD had 44% decrease in the occurrence of AREs. However, this group also had a small increase in the OAAS score during the procedure and increased recognition of image prompts during procedure and during sedation. There was no difference in image recall during procedure and during duration of sedation.

During this study, 104 of 107 procedures were successful. There were two unsuccessful procedures in the MS group (a distal radius fracture reduction and a lunate dislocation) and one in the DS group (a hip reduction); of the two unsuccessful procedures in the MS group, both achieved a deep level of sedation. The distal radius fracture reduction was successful after a second reduction attempt under sedation; the other two procedures required reduction under general anesthesia in the operating room.

DISCUSSION

The preprocedural assignment of a target sedation level did not lead to a difference in the rates of AREs or amnesia during PS in the ED. Patients randomized to DS were more likely to have more than one ARE with an effect size of 17%. Patients randomized to DS also had a 23% increase in the total number of AREs. Patients assigned to the moderate target sedation level achieved this sedation level only 50% of the time and 77% of the time for the DS target group. During this study, only the target sedation level was assigned and there were no specific propofol dosing guidelines for sedating physicians. This indicates that it is difficult to control the level of sedation, particularly when trying to achieve a lighter level of sedation, and could also indicate that the typical starting dose of propofol of 1 mg/kg might be excessive when trying to target MS. This also demonstrates that despite having a target sedation level, the achieved level of sedation is frequently different than the desired goal, which makes assigning a preprocedural target sedation level an unreliable tool to ensure a specific PS level.

It has already been established that patients who achieve MS have similar procedural recall and a trend toward decreased RD than those who achieve DS;[9] the current data support these prior findings. Previously, the largest randomized trial on this topic (n = 75 patients) was unable to determine if there was a difference in RD or amnesia caused by assigning a presedation target.[2] In the prior study, the smaller size

and poor separation of the randomization arms limited the strength of this conclusion. Our trial had a larger number of enrolled patients and also utilized the visual memory test to allow for a more robust assessment of amnesia.

There was a difference in AREs based on the level of sedation achieved. In patients who achieved DS, there was a 44% increase in patients that had one ARE, 26% increase in the need for more than one ARE, and 79% increase in total AREs. This effect was not related to dosage or propofol or number of doses of propofol given. Compared to achieving DS, those who achieved MS had a similar percentage of images freely recalled of the prompts provided, but did get 10% more answers correct on the image recognition quiz.

Assigning a target sedation level also did not change the rate of procedural recall or amnesia or the duration of amnesia. Thirty percent of patients did not recall an image after propofol despite appearing to reach their mental status baseline and easily being able to describe images. Patients were only able to correctly identify 64% of prompts on the multiple-choice test when they were alert enough to describe the image during the sedation. This suggests that that the memory-altering effects of propofol are not directly related to the apparent level of consciousness or the ability to verbally interact after propofol is administered. No patient recalled an image that they did not describe; however, some patients who did not appear alert were able to recognize multiple sequential images without being able to describe the image or subsequently recall them, which demonstrates that the ability of the patient to verbally interact and appear alert is not a sensitive measurement of the ability to form memories. During periods of time when a patient lost their end-tidal wave form or needed bag-valve mask breaths, jaw thrust, or sternal rub, no images were recalled.

Prior studies have postulated that there is a degree of retrograde amnesia associated with propofol PS.[10] In our study, patients were able to free recall images presented to them 30 to 60 seconds prior to the sedative dose. Patients could recall 42% of images from the start of the study prior to receiving any sedating drug. On average, patients continued to intermittently recognize images until 15 seconds before the propofol dose. It is possible that this difference is related to the increased ability of patients to recall visual prompts rather than verbal prompts used in previous research. Patients had near perfect scores (median = 100%, Table 1) on the recognition test prior to the start of the procedure indicating that the retrograde amnestic effects of propofol are present but variable and incomplete.

The return-to-baseline mental status after the procedure start was 13 minutes in both randomization groups; this is similar to prior studies on this subject.[10] There were no documented emergence phenomenon or other adverse events during patient recovery after the end of the procedure in either group.

There is not a described dose of propofol that can be used to reliably achieve MS or DS, and both levels have been described as achieved using similar doses. The MS target group had a 12% decrease in the initial dose and 18% decrease in the total propofol dose compared to the DS target group. Future studies using different initial doses based on these findings may help refine the current dosing recommendations for propofol.

Both randomization groups had a similarly high rate of RD. Eight patients required bag-mask ventilation during sedation; it was three times more likely that these patients were assigned to target DS, but this difference was not statistically significant. Only one of these patients received a propofol dose of >1.5 mg/kg. This illustrates the variable respiratory effects of propofol that can occur with typical doses and the necessity of vigilant airway monitoring for both moderate and deep procedural target sedation levels.

Analysis of the achieved level of sedation showed a clear relationship between DS and an increased occurrence of AREs. We also found increased image recognition after propofol and during the procedure in the MS group, but not of increased image recall or a difference in the patient reported recall and pain VAS scores.

The assignment of a target sedation goal of moderate did not result in that target level being consistently achieved. Despite this, however, assigning a target sedation level of moderate decreased the occurrence of multiple AREs. It does not, however, decrease the overall incidence of AREs, the rate of subclinical RD, procedural amnesia, patient satisfaction, patient perceived recall, patient pain, procedural difficulty, or procedure success rate. Further research into the factors that can result in the consistent achievement of moderate rather than DS with propofol may be useful for the development of sedation protocols with less respiratory events but consistent procedural amnesia.

LIMITATIONS

The independent variable in this study that is difficult to control is physician behavior. Sedating physicians

were assigned a target sedation level, but how they chose to deliver the drug to achieve that goal was up to physician discretion. It does appear that the sedating physicians in this study attempted to use less propofol as there was a significant difference between randomization groups. This study design was intended to resemble the clinical practice of the assignment of target sedation levels. It is unclear, however, if the difference in the rate of achieving the targeted goal of sedation between the moderate and deep groups is secondary to unpredictable drug effects or to physician compliance with the study protocol.

Our criteria used for defining RD have been used in several prior studies;[8,20,21] these indicate subclinical changes that indicate a patient has a change in their respiratory effort. Not all patients that meet this definition of RD experience clinically significant respiratory compromise. In this study, the prevalence of subclinical RD was higher than in prior studies (64%–70% vs. 49%), making it likely that our study was underpowered for our primary ARE outcome.

Another possible limitation is that, often when patients are deeply sedated they are unable to open their eyes, making visual prompt delivery impossible. During a prior study using verbal prompts,[12] no patients were able to recall a verbal prompt after the sedation that they did not repeat. Therefore, it is unlikely that we missed detecting patient memory formation during the period of time that the patients' eyes were closed.

Also, due to the fact that a variety of procedures were performed, some patients had significantly longer sedations than others. Because of this, some patients were presented with significantly more visual prompts and needed to retain memories for a longer period of time. However, given that the patients uniformly performed well on the image recognition test for the images seen prior to the sedation, this likely was not a significant barrier.

Although we did not detect a difference in our primary outcome of rate of AREs or procedural amnesia, we did detect a difference in the need for multiple AREs and total AREs. This indicates that there is likely a trend toward increased clinically significant AREs in the deep target sedation level group. The increased prevalence of RD in this study from our prediction and the difficulty with achieving the targeted sedation level made it more difficult to assess this. It is likely that a larger trial would be needed to detect differences in RD and amnesia, but it is likely that they exist as the differences were apparent when examining the achieved sedation level data.

CONCLUSIONS

In this randomized clinical trial, assigning a presedation target of moderate or deep sedation increased the need for multiple adverse respiratory events and increased total number adverse respiratory events, despite the fact that it did not reliably achieve the target sedation level. There was no difference in the number of patients who experienced an adverse respiratory event, visual prompt recall or recognition during the procedure, patient-reported pain, patient-reported recall, patient satisfaction, or procedural difficulty between the target groups. When examining the achieved level of sedation, MS was associated with a decrease in adverse respiratory events with a small decrease in procedural amnesia. Our study suggests that a target of moderate sedation provides adequate amnesia with fewer adverse respiratory events than a target level of deep sedation, even though it frequently results in the achievement of deep sedation.

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