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Bolus-Dose Fospropofol Disodium (Lusedra®): Is 10 mg/Kg Superior To 6.5 mg/Kg for Sedation in Patients Undergoing Regional Anesthesia Blocks Prior to Orthopedic Surgery?

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Abstract

Objective: Fospropofol disodium (Lusedra®) is a pro-drug propofol for Monitored Anesthesia Care. The FDA-approved dose regimen is minimally effective with a slow onset often requiring supplemental doses at 4 minutes to achieve adequate sedation and frequently requires early re-dosing. This study was designed to assess if a larger initial bolus dose of 10 mg/kg could achieve successful sedation without supplemental doses and without an increase in sedation-related adverse events.

Methods: An IRB-approved trial enrolled 12 adults undergoing elective orthopedic surgery with regional block. After IV fentanyl 50-75 micrograms, patients were randomly assigned into three IV bolus groups: fospropofol 6.5 mg/kg, fospropofol 10 mg/kg, or placebo with midazolam for rescue sedation if needed. Following the initial bolus, the level of sedation was measured, and if adequate, the block initiated or additional IV sedation injected before proceeding with the block.

Results: Hundred percent of the 10 mg/kg fospropofol group achieved appropriate sedation in less than 4 minutes compared to 50% of the 6.5 mg/kg group (P=0.048) and 40% of the fentanyl only participants with average times to sedation of 2.0 ± 0.0 minutes, 5.0 ± 4.0 minutes, and 7.0 ± 6.0 minutes, respectively. All of the 10 mg/kg group experienced deep sedation (MOAA/S 1-2), 60% experienced paresthesia or pruritus on bolus injection, 40% experienced delayed recovery from sedation, and 20% (1 of 5 patients) experienced a short period of apnea without hypoxemia. Sedation with midazolam produced delayed recovery in 40% of patients and 20% experienced deep sedation (MOAA/S 1-2).

Conclusion: 10 mg/kg bolus-dose fospropofol was 100% successful in producing sedation in less than 4 minutes, but was accompanied by deep sedation (p+0.048) and delayed recovery from sedation and more frequent apnea that make this dose unsuitable for procedures requiring short or minimal-to-moderate sedation. Further randomized trials with adequate power are required including consideration of an 8 mg/kg dose of fospropofol for MAC sedation procedures.

Keywords: Lusedra; Fospropofol; Regional anesthesia block; Monitored anesthesia care; Midazolam; Fentanyl; Conscious sedation

Abbreviations

CSC: Current Standard of Care; ASA: American Society of Anesthesiologists; PS: Physical Status; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; DCF: Data Collection Form; IND: Investigational New Drug; MOAA/S: Modified Observer's Assessment of Alertness/Sedation Scale; MAC: Monitored Anesthesia Care; O_2: Oxygen; SD: Standard Deviation

Introduction

In the current practice at Mayo Clinic Hospital and as elsewhere, the majority of patients undergoing any major orthopedic surgery (e.g. total joint replacement or repair) have a regional block with local anesthetics placed prior to their surgical procedure to provide additional intra- and postoperative pain control. An indwelling catheter may be left in place for continuous infusion of local anesthetics for one to two days postoperatively. To facilitate the precise insertion of the catheters, all patients receive minimal-to-moderate sedation during the block placement procedure.

The current standard of care (CSC) is a combination of an analgesic (IV fentanyl) with the sedative midazolam in almost 100% of cases. Midazolam dosing can be problematic due to wide variability in dosing and metabolism, respiratory depression, opiate potentiation, dose-responsiveness, emergence delirium, and delayed or prolonged wake-up.

Fospropofol disodium (Lusedra®) was developed for an indication of mild to moderate sedation in adult patients undergoing diagnostic or therapeutic procedures. Fospropofol is a water-soluble pro-drug that is rapidly metabolized to propofol following IV injection and is

FDA-approved (December 2008) for Monitored Anesthesia Care (MAC) [1-12]. Fospropofol may offer significant advantages over the current midazolam-fentanyl sedation routine if it can help achieve rapid and predictable adequate sedation without adverse events or wide variability in dose responses.

The current FDA-approved initial bolus dose of fospropfol 6.5 mg/kg was extensively studied to achieve sedation while minimizing the incidence of sedation-related adverse events. The targeted group for using fospropofol was non-anesthesia personnel administering mild-to-moderate (conscious) sedation. The small initial bolus-dose required clinicians to administer 1-2 additional supplemental doses in the majority of patients (>70%) no more frequently than every 4 minutes. This additional delay in time to initiate a procedure while waiting for the onset of sedation, and the required supplemental doses becomes inefficient, expensive, and unnecessary if a more appropriate larger initial dose can be demonstrated to maximize a single bolus-dose success while avoiding sedation-realted adverse events.

We hypothesized that a dose of 10 mg/kg would be a superior initial single bolus-dose of fospropofol to achieve successful and rapid initiation of sedation based on a review of earlier pre-submission dose-ranging studies using fospropofol (Eisai confidential documents).

The purpose of this study was to compare the current package insert approved initial 6.5 mg/kg IV bolus-dose of fospropofol with a 10 mg/kg IV bolus-dose for initiation of effective sedation prior to placement of a local anesthetic block. The initial study was planned to enroll at least 150 patients to fully compare the dosing regimens and monitor for sedation-related adverse events. Due to financial issues and company re-direction of resources, the sponsor requested the study be abruptly discontinued. At that point, the authors had just completed the first 12 patients. While no statistical power could be obtained, the data obtained is valuable when considering current practice routines, issues with the package insert dosing effectiveness, and needed refinement of the dosing of fospropofol for current and future MAC usage by anesthesia care teams.

Materials and Methods

Because the study bolus-dose was in excess of an FDA-approved fospropofol dose, the first author obtained a new IND (#108531) and Eisai funded a research grant for the clinical trial following IRB approval. Twelve ASA PS 2-3 adults, aged 57-84 years, with weights of 65.8-116.5 kg admitted for elective orthopedic surgery with a regional block prior to surgery were studied. The project statistician created the randomized treatment allocation schedule by using a computer random number generator. Inclusion criteria required patient to be ASA PS 1-4; able to understand and complete, either orally or in writing, the consent form and required assessments; and if female, the patient had to be surgically sterile, postmenopausal, or not pregnant or lactating and must have been using an acceptable method of birth control for at least 1 month prior to surgery, with a negative urine pregnancy test result at screening.

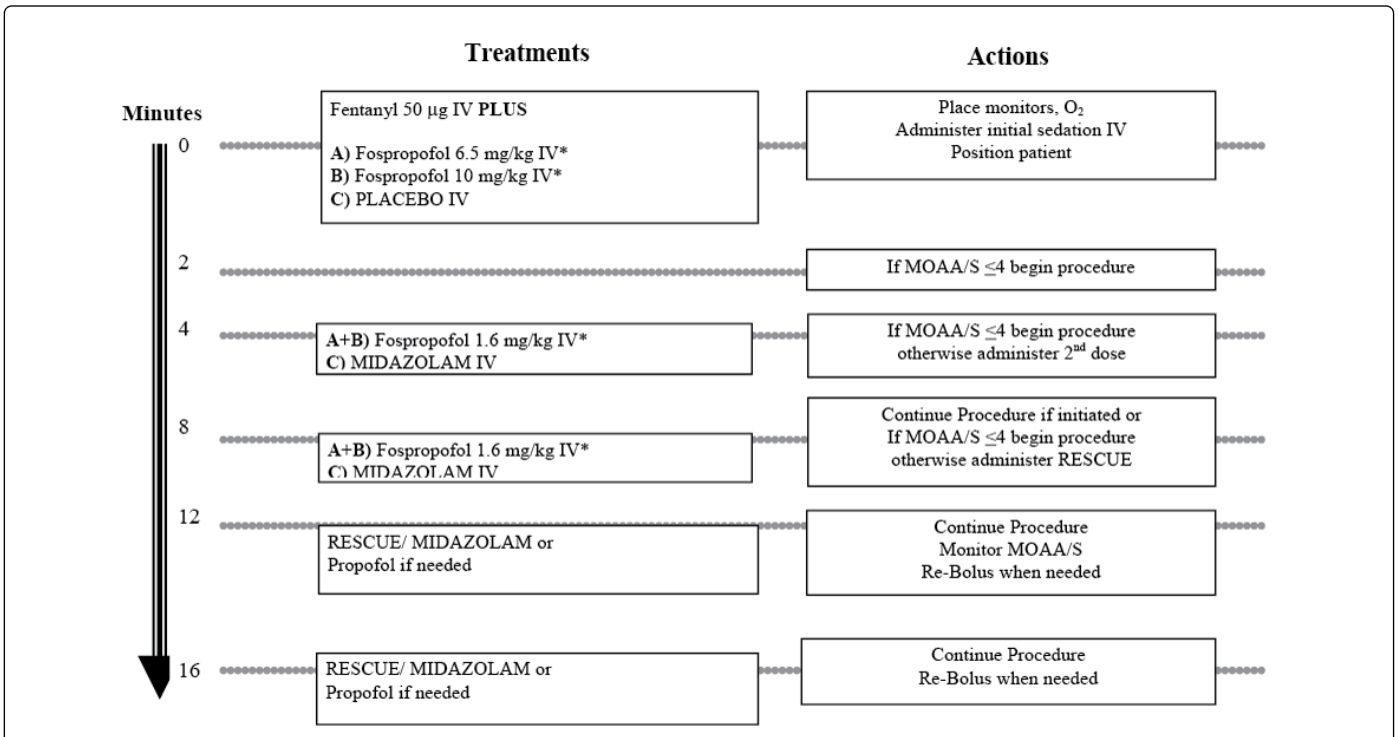

Figure 1: Fospropofol bolus-dose sedation study step-by-step timeline. *Dose reductions of 25% for ASA PS 3-4 and age>65; Dose weight limits of 60 to 90 kg. MOAA/S: Modified Observer's Assessment of Alertness/Sedation scale.

Exclusion criteria prevented enrollment of any patient with a history of allergic reaction or hypersensitivity to any planned study drug or anesthetic agent, opioid, or benzodiazepine; any patient for whom the fentanyl or midazolam injection was possibly contraindicated; and any patient unable to provide a post-procedural assessment of satisfaction or procedural recall due to pre-existing neurological disorder such as dementia.

Enrollment inclusion and exclusion criteria were verified from the online patient medical record during their preoperative assessment. Patients were recruited sequentially and were assigned to receive an initial bolus dose of IV fentanyl 50-75 micrograms and enter one of three IV study drug routines: fospropofol 10 mg/kg, fospropofol 6.5 mg/kg, or an initial placebo bolus. All study data were collected directly during the patient treatment episode and with a written survey tool the day following surgery. Hemodynamic (SBP, DBP, HR), and respiratory (pulse oximetry) data were collected from the bedside monitors (GE Solar 8000i). A Data Collection Form (DCF) was used to collect additional outcomes variables including any sedation or treatment-related adverse events from the time of drug administration until entry into the operating room following the block.

The block procedure began with application of nasal prong oxygen (2 L/min) and standardized monitoring. The initial dose of IV fentanyl was followed immediately by the assigned sedative delivered in a pharmacy-blinded syringe (26-milliliter total). A Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S - APPENDIX) assessment was made at 2 minutes and if adequate (MOAA/S<4) the block was initiated. The next MOAA/S assessment was made at 4 minutes and if adequate, the block initiated. If the patient was not adequately sedated, a second dose of fospropofol or the blinded midazolam rescue dose (for placebo group) was then administered in a pharmacy-blinded syringe (5-milliliter total) and a MOAA/S assessment made 4 minutes later. Midazolam dosing was based on weight: 1 mg for patients<60 kg; 1.5 mg for patients>60 to <90 kg; or 2 mg for patients ≥ 90 kg.

Any fospropofol initial bolus dose was reduced by 25% in patients with ASA PS 3-4 or age>65 (Modified Dosing Regimen) as recommended in the package insert. Patients weighing<60 kg were dosed at 60 kg while patients weighing>90 kg were dosed at a maximum of 90 kg. Assessments of MOAA/S determined the need for supplemental doses of fospropofol (1.6 mg/kg for either fospropofol group) or the midazolam for the placebo group to be administered as required to complete the block. The systematic study timeline is shown in Figure 1.

Results

Participant demographics including age, weight, ASA PS and male-to-female ratio are listed in Table 1 as averages including standard deviations. The 10 mg/kg fospropofol group consisted of 5 participants with male-to-female ratio of 3:2. The 6.5 mg/kg fospropofol group had only 2 participants with a male-to-female ratio of 2:0; the initial placebo group included 5 participants with a male-to-female ratio of 4:1. The average age and ASA PS of the groups were similar while the average weight varied from 77.2 ± 7.2 for the 10 mg/kg fospropofol group, 89.8 ± 2.5 for the 6.5mg/kg fospropofol group, and 91.2 ± 21.4 for the placebo-midazolam group.

The primary outcome was achievement of sedation within 4 minutes of administration of the initial bolus of study drug. As shown in Table 2, for the initial dose, 100% of the 10 mg/kg fospropofol group achieved sedation within 4 minutes compared to only 50% of the 6.5 kg/mg fospropofol group and 40% of the placebo group having received only fentanyl prior to midazolam rescue. Of the remaining placebo participants, the added IV midazolam produced adequate sedation in all patients. As noted, the fospropofol doses given were reduced in the pharmacy-blinded syringes by 25% for patients with an ASA PS 3-4 or over the age of 65. This modified dose was required in 80% of the 10 mg/kg fospropofol group and 50% of the 6.5 mg/kg fospropofol group.

	10 mg/kg Fospropofol (n=5)	6.5 mg/kg Fospropofol (n=2)	Placebo & Midazolam (n=5)
Age (years)	73 ± 7	72 ± 4	72 ± 12
Weight (kg)	77.2 ± 7.2	89.8 ± 2.5	91.2 ± 21.4
ASA PS (all participants 2-3)	2.8 ± 0.5	2.0 ± 0.0	2.4 ± 0.5
Male:Female	3:2	2:0	4:1
ASA PS: American Society of Anesthesiologists physical status			

Table 1: Demographics of each group. Data listed are mean ± SD.

	10 mg/kg Fospropofol (n=5)	6.5 mg/kg Fospropofol (n=2)	Placebo & Midazolam (n=5)
Participants achieving sedation within 4 minutes	5/5 (100%)	1/2 (50%)	2/5 (40%)
Dose 1 produced adequate sedation	5/5 (100%)	5/5 (100%)	2/5 (40%)
Dose 2 produced adequate sedation	NA	NA	1/3 (33%)
Additional sedative required	0/5 (0%)	0/2 (0%)	3/5 (60%)
Modified dose administered	4/5 (80%)	1/2 (50%)	NA

Table 2: Percentage of participants who achieved sedation within 4 minutes; required second dose; required additional sedative to complete nerve block.

The secondary outcomes measured included average time to sedation, recovery time from sedation, and adequate recovery from sedation prior to entry to the operating room. Average time to sedation for the 10 mg/kg fospropofol group was 2.0 ± 0.0 minutes, 5.0 ± 4.0 minutes for the 6.5 mg/kg fospropfol group and 7.0 ± 6.0 minutes for the placebo-midazolam combination group. Sixty percent of the 10 mg/kg fospropofol group recovered completely from sedation prior to entry to the operating room, compared to 100% of the 6.5 mg/kg fospropofol group and 80% of the placebo-midazolam combination group as shown in Table 3.

Serious adverse events did not occur in the 6.5 mg/kg fospropofol or placebo rescued with midazolam groups. One serious adverse event, apnea lasting less than a minute, occurred in one of the five 10 mg/kg fospropofol treated patients. The patient was managed with an assisted jaw thrust and repositioning of the head without developing hypoxemia (saturation<90%).

Deep sedation, defined as MOAA/S 1-2, occurred in 100% of the 10 mg/kg fospropofol group, 0% of the 6.5 mg/kg fospropofol group, and 20% of the placebo with rescue midazolam group. Delayed recovery from sedation occurred in 40% of the 10 mg/kg fospropofol group, 0% of the 6.5 mg/kg fospropfol group, and 40% of the placebo with midazolam for rescue group. The larger dose of fospropofol did not appear to produce more frequent or severe paresthesia or pruritus

upon injecton. It occurred in 60% of the 10 mg/kg fospropofol group, 50% of the 6.5 mg/kg fospropofol group and 0% of the placebo group as shown in Table 4. This incidence of discomfort on bolus injection matches the reported incidence in the package insert.

	10 mg/kg Fospropofol (n=5)	**6.5 mg/kg Fospropofol (n=2)**	**Placebo & Midazolam (n=5)**
Time to sedation (minutes)	2.0 ± 0.0	5.0 ± 4.0	7.0 ± 6.0
Recovery time from sedation or entry to OR (minutes)	20.4 ± 10.7	11.0 ± 4.2	14.8 ± 7.8
Participant recovered from sedation prior to OR entry	3/5 (60%)	2/2 (100%)	4/5 (80%)

Table 3: Recovery time from sedation or OR entry (whichever came first). Data listed are mean ± SD.

	10 mg/kg Fospropofol (n=5)	**6.5 mg/kg Fospropofol (n=2)**	**Placebo & Midazolam (n=5)**
Total other adverse events	5/5 (100%)	1/2 (50%)	2/5 (40%)
Deep sedation (MOAA/S 1-2)	5/5 (100%)	0/2 (0%)	1/5 (20%)
Delayed recovery from sedation	2/5 (40%)	0/2 (0%)	2/5 (40%)
Paresthesia or pruritus	3/5 (60%)	1/2 (50%)	0/5 (0%)

Table 4: Percentage of participants affected by reported adverse events.

				number of patients		
number of patients	**10 mg/kg**	**6.5 mg/kg**	**Placebo**	**Δ**	**95% CI**	***P***
N	5	2	5			
Demographics						
Age (y); mean (SD)	73.1 (7.8)	71.5 (4.3)	72.2 (11.6)	1.6 (7.2)	-14 to 17	0.81
Female	3 (60%)	0 (0%)	4 (80%)			0.43
Weight (kg); mean (SD)	77.2 (7.2)	89.8 (2.5)	91.2 (21.4)	-12.6 (6.5)	-27 to 1.4	0.07
ASA P3	4 (80%)	0 (0%)	2 (40%)	0.80		0.14
Sedation Outcomes						
Sedation within 4 min	5 (100%)	1 (50%)	2 (40%)	0.50	-0.26 to 0.99	0.29
Sedation with One Dose [a]	5 (100%)	2 (100%)	2 (40%)	0.00	-0.52 to 0.84	>0.99
Sedation with Two Doses	NA	NA	1/3 (33%)	NA	NA	NA
Additional Sedative	0 (0%)	0 (0%)	3 (60%)	0.00	-0.84 to 0.52	>0.99
Modified Dose	4 (80%)	1 (50%)	4 (80%)	0.30	-0.47 to 0.90	>0.99
Recovery Outcomes						
Time to Sedation (min) mean (SD)	2.0 (0.0)	5.0 (4.2)	7.4 (5.6)	-3.0 (1.9)	-7.1 to 1.1	0.07
Recovery Time (min) mean (SD)	20.4 (10.7)	11.0 (4.2)	14.8 (7.8)	9.4 (9.8)	-12 to 30	0.12
Recovered Prior to OR	3 (60%)	2 (100%)	4 (80%)	-0.40	-0.85 to 0.52	>0.99
Adverse Events						
Total Other	5 (100%)	1 (50%)	2 (40%)	0.50	-0.26 to 0.99	0.29
Deep Sedation	5 (100%)	0 (0%)	1 (20%)	1.00	0.07 to 1.00	0.048
Delayed Recovery	2 (40%)	0 (0%)	2 (40%)	0.40	-0.52 to 0.85	>0.99
Paresthesia or Pruritus	3 (60%)	1 (50%)	0 (0%)	0.10	-0.64 to 0.78	>0.99

Table 5: Statistical analysis of completed study patients' primary outcomes. [a]primary outcome measure.

Table 5 tabulates the statistical analysis of completed study patients' primary outcomes. The number achieving deep sedation with the 10 mg/kg dose did achieve statistical significance (p=0.048) even with few enrollees. The time to achieve the required level of sedation was also noted to be faster and almost achieved significance as well (p=0.07) despite the low number of patients.

Discussion

The primary outcome measure of this study was the percentange of participants who achieved adequate sedation (MAAO/S ≤ 4) within 4 minutes. The results show 100% of the larger dose of 10 mg/kg fospropofol group achieved sedation within 4 minutes without supplementation as compared to 50% of the 6.5 mg/kg fospropofol group and 40% of the placebo (IV fentanyl only) rescued with midazolam group (p=0.48). In terms of the primary outcome, the 10 mg/kg fospropofol was more effective than either the 6.5 mg/kg fospropofol bolus-dose or the use of fentanyl alone and adding midazolam as needed to achieve adequate sedation for the preoperative block.

Although the 10 mg/kg fospropofol dose was more rapid and the most successful in terms of the primary outcome measure, it was accompanied by more adverse events. The most serious of such events was 1 case of apnea lasting less than a minute – but also the only such event of the study. Further, 100% of the group experienced very deep sedation. This may or may not be appropriate for a procedure where some interaction with the patient may be required, such as reacting to needle stimulation directly in or on the peripheral nerve. It appears that the dose of 10 mg/kg of fospropofol, even with its modified dose of 7.5 mg/kg in older or "less medically-fit patients," may be too high for the intended purpose of minimal-to-moderate sedation due to its associated adverse events (deep sedation, delayed recovery from sedation, apnea). The study also confirms that the single dose of 6.5 mg/kg is often inadequate for a reasonably rapid onset of sedation when administered by anesthesia practitioners with specialized training to manage all of the potential sedation-related adverse events seen with such drugs as propofol itself, midazolam, and IV opioids. It may be that a dose between the 10 mg/kg studied and the 6.5 mg/kg approved dose may be a more ideal starting bolus to initiate appropriately rapid and safe MAC sedation. Additional studies are needed to determine the ideal dosing for various levels of required sedation from mild to moderate and to the deep levels as was produced in the 10 mg/kg group studied.

The primary limitation of this study is obviously the sample size limited due to a loss of funding with only an n=5 for the 10 mg/kg fospropofol group, n=2 for the 6.5 mg/kg fospropofol group, and n=5 for the midazolam comparator. The data as analyzed provide a cautionary note for clinicians who may be trialing larger initial doses of fospropofol if they have noted the 6.5 mg/kg dose to be frequently inadequate. Unlike the reversibility of respiratory depression from a benzodiazepine with romazecon, there are no reversal agents available for propofol or fospropofol.

In conclusion, although the limited sample size hinders statistical certainty in many variables of interest, in terms of the primary outcome of achieving sedation in less than 4 minutes, the 10 mg/kg fospropofol dose was more successful than the 6.5 mg/kg fospropofol bolus. However, induction of very deep sedation in 100% of the participants in the larger 10 mg/kg fospropofol group indicates this dose may not be suitable for procedures that require short or minimal-to-moderate sedation or if deep sedation is undesirable, potentially dangerous or unnecessary. Further, the serious adverse event of apnea occurring in one of the patients is noteworthy and may be an indication that the 10 mg/kg dose of fospropofol is not appropriate for routine use. Further studies investigating doses such as 8 mg/kg of fospropofol should be conducted with appropriate sample sizes and patient groups.

Declaration of Competing Interests

JBL received clinical research funding for this Investigator Initiated Study from Eisai Inc., 100 Tice Blvd. Woodcliff Lake, NJ, USA 07677. The Investigational New Drug (IND) number was 108531.

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