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The analgesic effects of subhypnotic doses of propofol in human volunteers with experimentally induced tourniquet pain

This double-blind, placebo-controlled study was performed to determine whether subhypnotic doses of propofol have analgesic or sedative effects.

Of 48 subjects randomly assigned to 1 of 4 bolus-infusion treatment groups, group 1 (n = 16) received propofol at 16 µg/kg per minute; group 2 (n = 16) received propofol at 32 µg/kg per minute; group 3 (n = 8) received 10% intralipids at 16 µg/kg per minute; and group 4 (n = 8) received 20% intralipids at 32 µg/kg per minute. Following a bolus of the study drug, a maintenance infusion was started and continued throughout the study. Thirty minutes after the study drug began infusing, an Observer's Assessment of Alertness/Sedation Scale was completed, a tourniquet was inflated, and a maximum tourniquet tolerance time (TTT) was obtained. Pain was assessed every 5 minutes while the tourniquet was inflated and immediately before deflation using a 0 to 10 verbally administered numeric rating scale (NRS). No significant differences in TTT were noted between the 2 propofol groups. However, the TTT for both propofol groups differed significantly from the control group (intralipid groups combined) (P<.05). There was a statistically significant difference in the time it took the propofol groups to reach a NRS score of 8 or greater when compared with the control group (P<.05). Sedation scores differed significantly between the control and the propofol at 32 µg/kg per minute groups (P<.05).

The results of this study suggest that propofol given at subhypnotic doses could serve as a valuable adjunct for acute postoperative pain management.

Key words: Analgesia, ischemic pain, propofol, tourniquet pain.

Myriad pharmacologic agents are available for the treatment of acute postoperative pain. While opioids are the mainstay of this therapy, they are not devoid of potential adverse effects, ranging from respiratory depression to constipation. Any drug that can have an opioid-sparing effect, without additional side effects, would be a valuable adjunct for practitioners who manage acute postoperative pain.

Reports in the literature of investigations of propofol as an analgesic in humans[1-5] have yielded equivocal results. In 1 early study that compared the analgesic effects of propofol with thiopentone using tibial pressure algesimetry, researchers reported the hyperalgesic effects of thiopentone, whereas propofol demonstrated a hypoalgesic effect.[1] Propofol also demonstrated analgesic effects for cold-pressure induced pain.[5] Conversely, later studies comparing propofol to thiopentone found that neither drug demonstrated any hyperalgesic effect in response to thermally induced pain or tibial pressure algesimetry.[2,3] In fact, 1 study reported that thiopentone had a greater hypoalgesic effect than propofol.[3] Thiopentone was, however, associated with more psychomotor impairment than propofol. Finally, propofol was shown to have a hyperalgesic effect on mechanically induced pressure pain when compared with alfentanil.[4]

One of the possible reasons for the disparities noted in these studies is the wide variability of intravenous (IV) propofol doses. In single-bolus injection studies where the responses to tibial pressure algesimetry and argon laser stimulation were measured, doses ranged from 0.25 mg/kg to 0.5 mg/kg.[1,2] Three separate studies using thermal, cold pressor, electrical, mechanical pressure, and cancer pain, achieved steady-state blood levels of the drug with initial boluses of 0.125 mg/kg to 1 mg/kg followed by continuous infusions ranging from 16.6 µg/kg per minute to 83.3 µg/kg per minute.[3-6]

No published studies investigate the analgesic effects of propofol using tourniquet tolerance as the method to induce pain experimentally. Using maximum tourniquet tolerance times (TTT) as a method of experimentally inducing pain was first introduced by Smith and colleagues[7] in 1966. While the mechanism of action of tourniquet-induced pain has been the subject of considerable debate, the most recent explanation involves pain transmission through both A delta and C fibers.[8] Because acute postoperative pain also is transmitted via these fibers, generalizing the results of this study to patients suffering from acute postoperative pain may be appropriate.

The present study tests the hypothesis that propofol given intravenously at subhypnotic doses would provide analgesia in human volunteers with experimentally induced tourniquet pain, with no clinically significant sedation. Therefore, the purpose of this study was to determine the analgesic and sedative effects of propofol administered intravenously at subhypnotic doses.

Methods
The 48 volunteer subjects, 30 men and 18 women, were recruited from the Naval Medical Center, Portsmouth, Va,

compound. The study was approved by the institutional review board at the Naval Medical Center. Exclusion criteria included a known hypersensitivity to propofol, intralipids, or any of their constituents; pregnancy; a history of abnormal lipid metabolism; increased triglycerides; bleeding disorders; cardiac disease; insulin-dependent diabetes mellitus; peripheral neuropathies or peripheral vascular disease; or history of surgery on either upper extremity. Women were required to have a negative result on a urine human chorionic gonadotropin specimen on the day they participated in the study. The subjects' participation was strictly voluntary; subjects were not paid, and no other forms of inducements were offered.

Following detailed explanation and informed consent, the subjects were randomly assigned by the pharmacy department via a random numbers table to 1 of 4 groups: (1) The propofol 16 group received a propofol 160 µg/kg bolus followed by propofol at 16 µg/kg per minute, diluted with 5% dextrose in water to 5 mg/mL, 50 mL. (2) The propofol 32 group received a propofol 320 µg/kg bolus followed by propofol at 32 µg/kg per minute, 10 mg/mL (undiluted), 50 mL. (3) The placebo groups received intralipid diluted to 10% with 5% dextrose in water, 50 mL; or (4) intralipid 20% (undiluted), 50 mL. The dosing regimen used in this study was chosen to minimize the sedative effects of propofol and maximize the potential analgesic effects. At the beginning of the study, subjects were informed that in order to limit excessive verbal stimuli, the investigators were only available to answer questions directly related to the study. All subjects were studied in an anesthetizing location, and electrocardiogram and pulse oximetry were monitored throughout the study.

After IV access was obtained with an 18 g IV catheter in the antecubital fossa, lactated Ringer's solution was infused to keep the vein open. Subjects then received a bolus of study drug or placebo over 2 minutes, followed immediately by a maintenance infusion of the drug via a calibrated infusion pump (model AS20GH, Baxter Healthcare Corp, Hookset, NH). This infusion continued throughout the study. The subject and the investigator were blind to the contents of the syringe. The preparation method of the study drug prohibited the investigators from discerning visual differences between the experimental drug and placebo. In addition, study drug preparation allowed the investigators to set the infusion device to deliver a bolus of 320 µg/kg followed by an infusion of 32 µg/kg per minute for all subjects. Immediately after the bolus, while the study drug was infusing, a 61 cm x 10 cm tourniquet (Zimmer, Inc, Warsaw, Ind)

was placed on the contralateral arm. The subject's upper arm had 2 layers of padding under the tourniquet. Thirty minutes after the infusion began, the tourniquet was inflated to 250 mm Hg using the ATS 1500 tourniquet system (Aspen Labs, Inc, Littleton, Colo). Subjects were instructed to notify the investigators when they could no longer tolerate the tourniquet. At that time, the tourniquet was deflated. A stopwatch was used to obtain the maximum TTT.

Thirty minutes after the infusion of the study drug began, and immediately before the tourniquet was inflated, the investigator completed the Observer's Assessment of Alertness/Sedation Scale (OAA/SS). This scale is based on a score of 1 = no response to tactile stimulation to 5 = wide awake. The OAA/SS has been demonstrated to be a valid, reliable tool that has been used in numerous studies.[9-15] The subjects also were asked every 5 minutes to rate their discomfort/pain while the tourniquet was inflated and immediately before deflation using a verbally administered numeric rating scale (NRS). This scale consisted of numbers from 0 to 10 where 0 was "no pain" and 10 was the "worst pain imaginable."

Once the maximum TTT was obtained, the infusion of the study solution was discontinued, and the study was completed. Following the completion of the study the subjects were observed for 60 minutes, then released with an adult attendant. They were required to have a companion accompany them from the department after the study was completed.

A statistical software package for the personal computer was used to analyze the data (SPSS, Springfield, Ill). Descriptive statistics and frequency distributions were used to examine the data. A chi square test was used to examine differences between groups regarding gender. Differences between the groups with regard to age, weight, and sedation scores were examined using Kruskal-Wallis tests, and Mann-Whitney tests were used to examine pair-wise comparisons when indicated. The log-rank test was used to determine differences between the 3 groups regarding TTT, time to obtain a NRS score of 8 or greater, and the time that a NRS score of 8 or greater could be tolerated. The number of participants in each of the 3 groups were as follows: propofol 16 (n=16, 33%), propofol 32 (n=16, 33%), and control (the 2 intralipid placebo groups combined, n=16, 33%). A significance level of $P < .05$ was considered significant for all statistical analyses.

Results
All of the subjects completed the study without problems or sequelae. With no statistically significant differences noted, the data from both placebo groups

were combined to form 1 group. The maximum allowable TTT of 60 minutes was exceeded by 4 of the subjects. As a result, median TTT were noted. The results of a chi square analysis demonstrated no statistically significant gender differences among groups (Table 1). In addition, no statistically significant differences were noted among the groups regarding age or weight (Table 2).

A Kaplan-Meier curve noted statistically significant differences in the TTT between the experimental (propofol) and control (intralipid) groups. Median time for the control group was 25.42 ± 0.93 minutes, while the median time for the propofol 16 group was 28.47 ± 9.72 minutes ($P=.04$), and the median time for the propofol 32 group was 43.42 ± 11.75 minutes [($P=.002$), (Table 3)]. As illustrated in Figure 1, after 30 minutes of total tourniquet time, 70% (n=11) of the subjects in the propofol 32 group still had the tourniquet inflated, while only 20% (n=3) of the subjects in the control group had the tourniquet inflated.

A Kaplan-Meier curve noted statistically significant differences between the groups in the time it took to obtain an NRS score of 8 or greater. The median time was 20 ± 4 minutes for the control (intralipid) group, 35 ± 6 minutes for the propofol 16 group ($P=.02$), and 40 ± 4 minutes for the propofol 32 group ($P=.009$) (see Table 3). In addition, the Kaplan-Meier curve demonstrated no statistically significant difference in the time that any of the subjects could tolerate the tourniquet once a pain intensity score of 8 or greater was obtained. The median time that all of the study subjects could tolerate an NRS score of 8 or greater was 10 minutes. As illustrated in Figure 2, after 30 minutes of tourniquet time, 60% (n=10) of the propofol 32 group still had not reached an NRS score of 8 or greater, while only 20% (n=3) of the control group had not obtained an NRS score of 8 or greater.

Results of the Mann-Whitney tests demonstrated no statistically significant difference in sedation scores between the propofol 16 group compared with the control group or the propofol 16 group compared with the propofol 32 group. However, there was a statically significant difference in the sedation scores of the propofol 32 group compared with the control group ($P=.004$) (Table 4).

Discussion

These data clearly suggest the analgesic properties of subhypnotic doses of propofol administered intravenously using an experimental pain model. Subjects in both of the experimental groups tolerated the tourniquet significantly longer than the control group and took significantly longer to reach a pain intensity

Table 1. Chi-square analysis of sex

	Propofol (16 µg/kg per min)	Propofol (32 µg/kg per min)	Intralipids (placebo)
Men	14*	8	8
Women	2	8	8

* No statistically significant difference noted between men and women subjects.

Table 2. Demographic data

	Mean	Minimum	Maximum	Range	SD
Age (y)	28.54	19	50	31	8.84
Weight (kg)	78.9	51	111	60	13.91
Sex	Men = 30		Women = 18		

Table 3. Median total tourniquet tolerance time

|	Control (intralipid)	Propofol (16 µg/kg per min)	Propofol (32 µg/kg per min)
Total tourniquet tolerance time (min)	25.42 ± .93	28.47* ($P = .04$) ± 9.72	43.42* ($P = .002$) ± 11.75
Time to reach a NRS† score of 8 or greater (min)	20 ± 4	35* ($P = .02$) ± 6	40* ($P = .009$) ± 4
Time at a NRS score of 8 or greater (min)	10	10	10

Note: All times are median times.
* Represents statistically significant values compared to control group
† NRS indicates numeric rating scale.

score of 8 or greater. Researchers have suggested that the analgesic properties are secondary to the sedative properties of propofol. Our data refute this assertion. If the propofol had rendered the subjects indifferent to the pain, the experimental groups should have been able to tolerate an NRS of 8 or greater for a significantly longer period of time than the control group. This clearly was not the case. While there was a statistically significant difference in the sedation scores between the control group and the propofol 32 group, we believe that the differences were not clinically significant. All subjects were easily arousable to verbal stimuli throughout the study.

Figure 1. Survival curve showing the percentage of subjects in each treatment group able to tolerate the tourniquet by 10-minute intervals
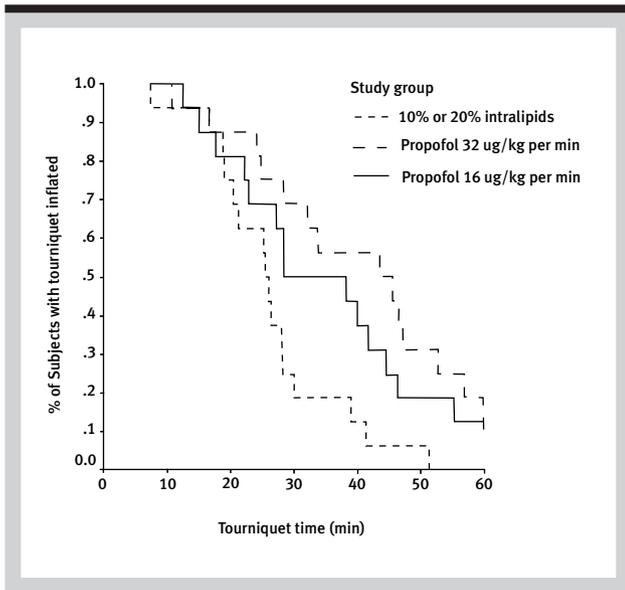
Figure 2. Survival curve showing the percentage of subjects who had not reached a numerical rating scale (NRS) score of 8 or greater by 10-minute intervals
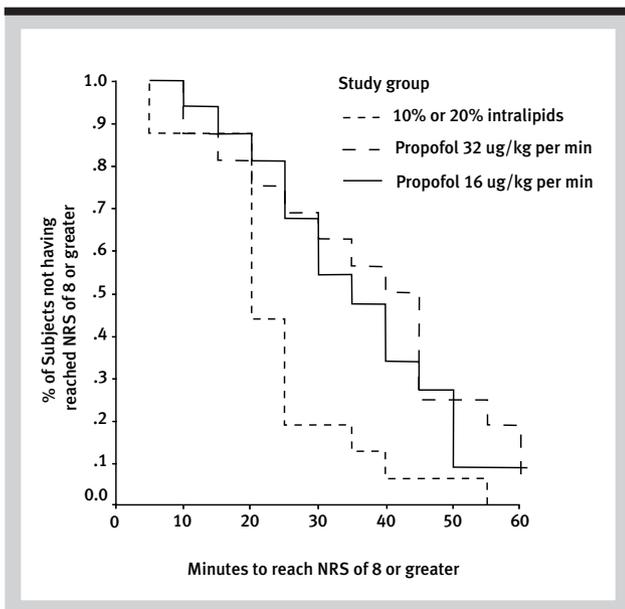
There are several possible explanations for the analgesic effects of propofol seen in the present study. First, no other study investigating the analgesic properties of propofol has used tourniquet tolerance for their experimental model. Because the scientific understanding of the physiology of pain transmission is constantly evolving, it is difficult to know exactly how different experimental models transmit pain. While experimentally induced pain is inexpensive

Table 4. Mean sedation scores (0-5 scale)

Sedation	N	Minimum	Maximum	Mean	SD
Group 1 16 µg/kg per min	16	4	5	4.63	0.5
Group 2 32 µg/kg per min	16	3	5	4.25* (P=.004)	0.68
Group 3 placebo	16	4	5	4.88	0.35

* Represents statistically significant value compared to control group

and convenient for the laboratory setting, its ability to exactly reproduce the physiology of natural pain transmission must remain suspect. It is however theorized that propofol interacts with the $GABA_A$ receptor/chloride channel complex and may influence the release of both glutamate and aspartate centrally.[16-17] It also has been suggested that propofol may cause the release of endogenous opioid peptides that bind with delta opioid receptors in the spinal cord.[17]

Potential limitations of the present study pertain to methodological considerations and design. One obvious limitation may be the presence of some selection bias. Even though attempts were made to recruit from the entire compound, the majority of the subjects were recruited from the Naval Medical Center. Of the total sample, 13 (27%) were anesthesia providers. We believe that randomization minimized this limitation because out of the 13 anesthesia providers, 4 received propofol 16 µg/kg per minute, 5 received propofol 32 µg/kg per minute, and 4 received placebo.

It is difficult to speculate exactly what influence, if any, their profession had on the results. However, because these subjects have an intimate knowledge of the pharmacodynamics and pharmacokinetics of propofol, some selection bias cannot be ruled out. Anecdotally, before the initiation of the study, 2 anesthesia providers were administered the 32 µg/kg per minute dose of propofol with the associated initial bolus. Neither of the providers discerned any noticeable difference in their level of sedation or the presence of a "burning" sensation when the propofol was administered. The remainder of the sample were hospital staff with no knowledge of propofol.

The age of the subjects could have influenced the results of the present study. While the mean age of the subjects was 28.5 years, 65% (n=30) of the subjects were younger than 30 years of age. Even though no literature suggests that age is related to tourniquet tol-

erance, some of the younger subjects may have viewed this experiment as a personal challenge. As such, they may have tolerated the tourniquet longer than otherwise expected.

While there was no statistically significant difference between the groups with regard to gender, 14 subjects in the propofol 16 group were men, and 2 were women. The propofol 32 and the control groups were equally divided between men and women.

Finally, no NRS scores were taken after the tourniquet was released. Transient pain is common after tourniquet release. It would have been interesting to note the incidence of this type of pain and whether subhypnotic doses of propofol would have influenced the perception of this pain.

The IV administration of subhypnotic doses of propofol could be used as an adjunctive medication in patients with acute postoperative pain. Moving this experiment from healthy human volunteers to patients with acute pain would be a logical first step in future research. Even though most acute pain can be successfully managed with opioid pharmacotherapy alone, the adverse effects associated with their use can range from bothersome urticaria to life-threatening respiratory depression. Propofol's potential opioid-sparing effects may allow patients to decrease their dose of opioids without decreasing their level of comfort.

In order to optimize the analgesic effects at a given dose, research correlating the degree of analgesia with a given IV dose would be extremely beneficial. In addition, research should be conducted to determine whether propofol has a ceiling effect and the dose where effective analgesia is limited by undesirable levels of sedation. Possessing this knowledge, the practitioner would be able to maximize the analgesic effects of propofol without compromising the patient's level of sedation.

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