

# Impact of Intravenous Injection Site on Children's Pain Experience with Propofol Administration

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## Abstract

**Purpose:** Propofol injection is associated with significant pain in children. This prospective, randomized, observational study assessed the pain experienced by children at the antecubital fossa versus the dorsum of the hand.

**Methods:** 136 children from 1-18 years old who were American Society of Anesthesiologists (ASA) class I-II and undergoing sedation with propofol for Magnetic Resonance Imaging (MRI) were included. They were sorted into two groups depending on IV site. Pain was evaluated using the 10-point Face, Legs, Activity, Cry and Consolability (FLACC) scale. FLACC scores were evaluated in pre-sedation before entering the MRI suit, in the MRI machine room pre-sedation, and upon administration of the propofol. Chi square and t-tests helped determine the differences in patient characteristics when comparing the two intravenous (IV) site groups. Group differences in FLACC scores were evaluated with Wilcoxon Signed Ranks and Wilcoxon Rank Sums tests.

**Results:** Admission and MRI room FLACC scores were not statistically significant by IV site. With propofol, FLACC scores for the hand IV site (median = 5, mean =4.93) were significantly higher than for the antecubital site (median =3, mean=3.34) (p=0.004).

**Conclusion:** Pain experience during propofol administration in antecubital fossa veins is significantly less than the dorsum of the hand.

**Keywords:** Propofol; Pain; FLACC; Injection; Conscious sedation;

## Abbreviations

ASA – American Society of Anesthesiologists

MRI- Magnetic Resonance Imaging

IV - Intravenous

FLACC - Face, Legs, Activity, Cry and Consolability

ED – Emergency Department

LCT - long chain triglycerides

MCT- medium chain triglycerides

NS – Normal Saline

WSR - Wilcoxon Signed Ranks tests

WRS - Wilcoxon Ranked Sums tests

CHEOPS - Children's Hospital Pain Scale

WBFS - Wong-Baker Faces Scale

## Introduction

Propofol (2, 6-diisopropylphenol) is an intravenous anesthetic/sedative agent with a rapid onset of action and is easily titratable [1]. It has been used extensively in the operating room and sedation venues including radiology, the emergency department (ED), and the intensive care units [2]. Propofol is manufactured in a lipid emulsion derived from egg whites [3]. It is the lipid carrier and emulsion of free propofol in the aqueous phase which plays a role in causing pain on injection. This is evidenced by studies citing a reduction in children's discomfort upon receiving serial dilutions of propofol [4-6]. Pain with propofol is prevalent in about 70% of adults [7] and up to 85% of children [8] thus heavily limiting its use in the pediatric population [7-10].

The pain is so uncomfortable that it has been ranked as the seventh most important drawback in current practice of clinical anesthesia by American anesthesiologists [11]. Different methods have been implemented to prevent the sharp and achy burn on injection for children. These include pretreatment with lidocaine [12], a ketamine-propofol admixture [13], formulations of Long Chain Triglycerides (LCT) versus Medium Chain Triglycerides (MCT) in propofol [4-5, 14-16], MCT vs LCT with added lidocaine [4,16,17], and opioids like alfentanil/remifentanil [10,18]. Significant advances in improving pain have been obtained. However, they have been inconsistent due to variability of protocols for medication administration, differing pain scales, and varying patient ages.

This topic is important because painful injection is undesirable for children, yet it is more probable due to the size of their accessible veins. After reviewing the cited studies looking at the effects of different medications administered, one realizes that most studies are accomplished using the dorsum of the hand. A few reports only ever use the antecubital fossa even though anesthesiologists believe that using larger caliber veins are naturally less irritating to the pediatric patient. To compare both IV sites simultaneously and formally investigate this belief held in clinical practice, we conducted a prospective, randomized, observational study

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in children. We wanted to assess the difference in pain experienced with propofol injection at the antecubital fossa versus the dorsum of the hand.

**Materials and Methods**

After obtaining the approval from the Institutional Review Board, a consecutive sample of all children ages 1-18 years old, ASA-PS I–II, undergoing elective sedation to complete Magnetic Resonance Imaging (MRI) without any contraindication to propofol sedation, was approached. Informed consent/assent was obtained from the patients and their parents. The children were patients of St. Christopher’s Hospital for Children in Philadelphia, PA. The timeline of the study was from January 2013 to July 2013. Patients with severely impaired neurologic function, global developmental delay, psychological disorders, or on analgesics or sedatives were excluded from this study (Table 1).

No patients had received any premedication(s) before their arrival in the MRI room or analgesics within twenty-four hours before sedation. We applied EMLA cream on either the antecubital area or the dorsum of the hand thirty minutes before trying to gain IV access. A 22-gauge catheter was inserted for venous access at approximately thirty minutes before starting the sedation. The designation was based on the insertion site as dorsum of the hand or antecubital fossa.

This was a prospective, randomized, and observational study. Therefore, patients were randomized based on alternate sedation days for initial IV attempts in the antecubital fossa or the dorsum of hand. All drugs were prepared and stored at room temperature and used within thirty minutes of preparation. On arrival in the MRI room, patients were routinely monitored and managed per hospital sedation policy. Propofol (LCT only emulsion) bolus dose of 1mg/kg was administered followed by a flush of normal saline (NS) to push the propofol through the IV line. A maintenance rate was started after the NS flush with the propofol dose adjusted to keep the patient comfortable and moderately sedated.

Pain was assessed by nurses independent of the study using the 10-point Face, Legs, Activity, Cry And Consolability (FLACC) scale [19,20] during injection (Figure 1). FLACC scores were assigned in three instances: in the pre-sedation assessment room, in the MRI machine room, and upon administration of the bolus dose of propofol (LCT only emulsion). The FLACC scores were measured three times for all patients (Figure 1). The admission nurse was responsible for all three score measurements. Per our protocol if the nurse failed to get the IV in the randomized/assigned site on two trials, the nurse would then have the freedom to choose an alternative site for IV access. A smaller 24-gauge catheter was not used for difficult sticks per this specific protocol.

7. Pain score (FLACC scale)	Admit	in room	Injection
<b>Face</b>			
0- No particular expression or smile			
1- Occasional grimace or frown, withdrawn, disinterested			
2- Frequent to constant quivering chin, clenched jaw			
<b>Legs</b>			
0- Normal position or relaxed			
1- Uneasy, restless, tense			
2- Kicking, or legs drawn up			
<b>Activity</b>			
0- Lying quietly, normal position, move easily			
1- Squirming, shifting back and forth, tense			
2- Arched, rigid or jerking			
<b>Cry</b>			
0- No cry ( awake or sleep)			
1- Moans or whimpers; occasional complaint			
2- Crying steadily, scream or sobs, frequent complaints			
<b>Consolability</b>			
0- Content, relaxed			
1- Reassured by occasional touching, hugging or being talked to, distractible			
2- Difficult to console or comfort			
<b>Total score:</b>			

**Figure 01:** FLACC scores measurement audit tool

## Statistical analysis

Differences in the distribution of sex, age, weight, number of attempts to gain IV access comparing IV sites were assessed with chi-squared and independent samples t-tests. Since FLACC scores were not normally distributed and we consider these ordinal data, non-parametric tests were used to explore differences in pain experience. Paired analyses--Wilcoxon Signed Ranks tests (WSR) -- tested differences in pain at admission, in the MRI room, and during propofol administration for the total sample. Wilcoxon Ranked Sums tests (WRS) were used to compare pain at IV sites at these three phases. A p-value < 0.05 was what was deemed to be statistically significant.

## Results

There was a total of 136 children in the study. Patient characteristics are summarized in Table 1. Sex of the child, age, weight, and number of attempts in placing the IV were not significantly different between sites. Mean age was 77.2 +/- 39.5 months and weight 26.9 +/- 16.3 kg. IV site groups were not significantly different in gender allocation, mean age or weight.

FLACC scores comparing the three measured stages of the sedation event for the combined sample and by IV sites are provided in Table 2. Table 2 also separates the FLACC scores into the 68 IV sites for the antecubital fossa and the dorsum of the hand respectively. FLACC scores were low and, clustered around 0 – 1 in admission and the MRI room. However, although the median FLACC scores were 0 at both phases, rankings were significantly higher (WSR  $p < 0.001$ ) for the MRI room than at admission (78% scored 0 at admission versus 56% in the MRI room). The difference is indicated by the higher mean in the MRI room (1.6 +/- 2.4 versus 0.8 +/- 1.9). As we expected, FLACC scores were substantially greater during propofol administration (median=5, mean=4.1 +/- 3.3) compared to admission and the MRI room (WSR  $p < 0.001$ ).

Pain/distress experience at admission and in the MRI room was not different when comparing IV sites. During propofol administration; however, the pain response was significantly greater in the hand site (median FLACC score = 5, mean = 4.9 +/- 3.2) compared to the arm (median 3, mean 3.3 +/- 3.3) ( $p = 0.004$ ).

**Table 1: Patient Characteristics**

	Antecubital Fossa	Dorsum of Hand	Total	P value
Gender				
Female	35 (51.5%)	37 (54.4%)	72 (52/9%)	
Male	33 (48.5%)	31 (45.6%)	64 (47.1%)	0.731 <sup>1</sup>
Age – months ( SD)	82.6 (36.8)	71.7 (41.6)	77.2 (39.5)	0.11 <sup>2</sup>
Weight – kg (SD)	28.3 (14.8)	25.5 (17.6)	26.9 (16.4)	0.32 <sup>2</sup>
Number of Attempts (SD)	1.2 (0.5)	1.4 (0.6)	1.3 (0.6)	0.15 <sup>2</sup>

<sup>1</sup>ChiSq Test <sup>2</sup>T-Test

**Table 2: FLACC Scores Comparing IV Sites**

	Sites combined (n=136)		Antecubital Fossa (n=68)		Dorsum of Hand (n=68)		P value <sup>2</sup>
	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	
Admission <sup>1</sup>	0	0.8 (1.9)	0	0.7 (2.0)	0	0.9 (1.8)	0.24
MRI Room <sup>1</sup>	0	1.6 (2.4)	0	1.7 (2.7)	0	1.6 (2.2)	0.87
Propofol Admin <sup>1</sup>	5	4.1 (3.3)	3	3.3 (3.3)	5	4.9 (3.2)	0.004

<sup>1</sup> Wilcoxon Signed Ranks Tests: Admission < MRI Room < Propofol Admin,  $P < 0.001$  for all pairs

<sup>2</sup> IV Site Comparisons -Wilcoxon Rank Sums Tests

## Discussion

The experience of pain upon the injection of propofol has been widely investigated and is reported to occur in approximately 70% of patients when given without any other treatment [7]. For this reason, further understanding of this topic is necessary as pain has been attributed to various factors. Some include the amount of free propofol in the aqueous phase of the emulsion, activation of the kinin-kallikrein system, site and speed of injection, and temperature of the preparation to name a few [4].

Several strategies in adults have been investigated as to their effects on alleviating pain. These include pre-injection administration of opioids [21], ketamine [13], metoclopramide [22], acetaminophen [23], or by cooling/warming the emulsion [24]. The most effective analgesic method though was IV lidocaine given as a Bier block before propofol [7]. Apart from medications, selection of an antecubital vein instead of a hand vein was numerically one of the most efficacious interventions in adults [25].

Avoiding pain on propofol injection especially in preschool children is even more desirable as pain appears limiting to an otherwise useful method of inducing sedation. The incidence of discomfort has reported to be in the range of 30-90% [16]. In children, strategies investigated for pain alleviation have centered mostly on formulations of propofol with MCT-LCT vs LCT alone, opioids, ketamine, implementation of lidocaine with MCT-LCT propofol, and cooling of the propofol solution. Despite these number of methods tested in children, the occurrence of pain has remained at 10-30% [16] and studies mostly focus on using the veins of the dorsum of the hand. The studies looking at MCT vs LCT have produced conflicting results concerning the efficacy of the MCT-LCT propofol formulation. Some have cited improvement with simply using the MCT-LCT formulation alone and even better results with lidocaine while others claimed that the mixed formulation was worse than LCT alone [4-5, 14-17]. Propofol mixed with alfentanil was effective in reducing pain; however, it did not completely abolish it [10,18].

Review of the literature showed that IV placement in these pediatric studies mostly used the dorsum of the hand instead of the antecubital fossa despite the promising findings of utilizing the antecubital vein in adults [25].

These studies also mostly focused on the dorsum of the hand even though many anesthesiologists already believe that using larger caliber veins would naturally be less painful. Recognizing this discrepancy in studies hoping to reduce pain on propofol injection by still using a more irritating and smaller caliber vessel, we believed there was still value to investigating the topic. To our knowledge there have not been any published studies with children that measured the pain of propofol injection in the antecubital fossa compared to the dorsum of the hand. Therefore, we conducted this prospective study in efforts of confirming what has been seen in the adult population [25] and supported by anesthesiologists in practice.

The results of our analysis demonstrated that the pain experienced during propofol administration in the antecubital vein was significantly less than in the dorsum of the hand. From a physiological standpoint, differences in vein diameter, flow rate, and endothelial structure might account for the reduction in pain. Presuming that propofol is injected mid-stream into the lumen of the vein, the larger diameter of and faster flow rate through the antecubital vein will minimize the extent to which a high concentration of propofol encounters the sensitive endothelial wall. Alternatively, propofol may be buffered more effectively when more blood is available to dissipate and mask the “full effect” of the bolus. Additionally, the composition of nociceptors along the endothelial wall might differ between the smaller veins of the hand and the larger antecubital veins [26-28].

Despite having a physiological explanation for greater pain sensed in the veins of the hand, some may still argue against the use of an antecubital vein in children based from experience with adults. The potential issues associated with the antecubital vein for the IV include occlusion when the elbow is flexed and delayed detection of extravasations relative to the dorsum of the hand. These concerns are legitimate; however, they may be less prominent in the pediatric population since a child's IV site can be fixed by a simple arm board. Likewise, the provider may hold the child's hand while pushing the propofol bolus.

The implications of our findings highlight and confirm that accessing larger caliber veins like in the antecubital fossa will elicit less pain than those in the dorsum of the hand. Limitations in our study include it being observational and not entirely randomized. Observational studies make important contributions to medical knowledge. However, unlike randomized controlled trials, they do not allow for the comparable distribution of both known and unknown factors in the groups to be compared [29]. By the same token, there are concerns for selection bias, confounders, information bias, measurement errors, and even observer bias [29].

Observer bias was a factor to be aware of in our study because multiple nurses conducted the FLACC score assessment. Although FLACC sub-scores for each category are well detailed and interrater reliability is supported by adequate kappa statistics for all items and for the total FLACC scores [19], subtle differences in scoring were still possible. The nurses conducting FLACC scores were independent of the study which may have decreased some of the observer bias; however, one must recognize that this type of bias is not typically intentional. It can simply involve slight changes in how the researchers interact with subjects and what observers choose to see [30]. In addition to the potential for bias with the FLACC scale, it is worth mentioning that the scale is valid for children in the ages of five to sixteen [19]. Recalling our experimental design, we assessed patients from one year to eighteen years of age thus

calling into question the validity of the FLACC scale for those from one to under five years old.

Another reservation to consider is under what environmental circumstances the FLACC assessment was done. For example, FLACC scores were less at baseline in the admission area which may have been possible since parents could physically console the child. This differs with parents not being allowed to accompany the patient in the MRI area pre- and during sedation hence leading to the children becoming even more inconsolable.

The subject of gauging pain continues to be challenging because children from varying ages are used as participants, and they have different ways of expressing their discomfort. Pain scores such as the FLACC were used here and in other studies; however, additional scales such as the Ontario Children's Hospital Pain Scale (CHEOPS) and the Wong-Baker Faces Scale (WBFS) have been cited [4,16]. Other ambiguous scales have been incorporated in similar studies such as a four-graded pain scale [17] and even one monitoring only spontaneous verbal and motor reactions [5]. The problem with different scales is that it allows for greater variability in what pain is truly detected as and that may become further magnified if more than one scale is adopted in a single study [16]. With that being said, there is not one single scale that has been validated for the use of children one year of age through adolescence and adulthood.

Another facet to the complexity of evaluating pain in these studies is the topic of premedications prior to surgery. The goals of premedication encompass anxiolysis and analgesia [31]. Anxiolytics are less commonly prescribed than other premedications, but they are useful for anesthetic cases especially in the pediatric population [31,32]. Examples include the unduly anxious child, the child presenting for repeated procedures at short intervals, and the child with learning difficulties with whom it may be difficult to gain rapport [31]. Despite the anxiolysis of benzodiazepines and the rapid return of normal mental function [31], one must recognize that premedications like 5-10mg of diazepam even 1 hour before anesthesia [15] may cloud the pain assessment.

We believe that our findings of FLACC scores for the hand IV site (mean =4.93) being significantly higher than the antecubital site [(mean=3.34) (p=0.004)] strongly confirms the advantage of using an antecubital IV for sedation with propofol. For future studies, it would be worthwhile to compare the pain felt with propofol alone through an antecubital IV versus that of a propofol combination with an opioid (remifentanyl/alfentanil) or ketamine via the antecubital IV. The antecubital arm IV groups could contain those receiving propofol alone, and then a separate subset of those with the MCT-LCT formulation of propofol or propofol (LCT) plus an opioid or ketamine. If desired, one could compare these interventions in the antecubital arm IV with those of a group looking at the dorsum of the hand.

For this future study, we would continue recommending against premedications. Since expression of pain is different across an array of ages, a more accurate overall analysis may require dividing children into ages one to five for a pain scale and five and above for another. For example, the CHEOPS can accurately be used for children ages one to five, and the FLACC for children ages five to sixteen. Statistical analysis could effectively compare the multiple groups. Another consideration for study design is to look at a comparison of pain experienced with 22-gauge IV catheters versus 24-gauge IV catheters. The smaller radius of a 24-gauge catheter relative to a 22-gauge catheter will result in less flow through the IV and could consequently result in more pain.

## Conclusion

Our findings demonstrated that the pain experienced during propofol administration in the antecubital fossa was significantly less than the

dorsum of the hand. The topic of propofol induced pain in children continues to be significant because up to 85% feel discomfort [8] with its use, and 10-30% still experience the sharp ache despite medication adjuncts to propofol [16]. It does not seem like medicine alone will eliminate the pain, but more than likely a multi-faceted approach will decrease the discomfort to less than the 10-30%. This is where we believe that going first for antecubital IV access in addition to previously studied adjunct medication to propofol can make a bigger impact than medication alone. Our overall goal is simply to seek other options for the already stressed and scared child.

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