# Prospective Randomized Crossover Evaluation of Three Anesthetic Regimens for Painful Procedures in Children with Cancer

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**Objective** To identify the most effective sedation regimen for bone marrow aspiration and lumbar puncture procedures with a prospective trial of 3 combinations of sedation/analgesia.

**Study design** In this double-blind crossover study, we randomly assigned 162 children with acute lymphoblastic leukemia or lymphoblastic lymphoma to receive fentanyl 1 mcg/kg, fentanyl 0.5 mcg/kg, or placebo, in addition to propofol and topical anesthetic for 355 procedures.

**Results** We found no significant differences among the 3 regimens in the frequency of pain (pain score > 0) or severe pain (pain score ≥ 5) during recovery, or a >20% increase in hemodynamic/respiratory variables during anesthesia. Treatment with fentanyl 1 mcg/kg was associated with a lower frequency of movement during procedure compared with treatment with fentanyl 0.5 mcg/kg ($P$ = .0476) or treatment with placebo ($P$ = .0545). The placebo group required longer time to recover (median, 18 minutes) compared with the fentanyl 0.5 mcg/kg group (median, 9 minutes) (median difference 2.0, $P$ = .007) and the fentanyl 1 mcg/kg (median 8 minutes), (median difference 2.0, $P$ = .15). The placebo group also required larger total dose of propofol (median 5 mg/kg) compared with that of the fentanyl 1 mcg/kg group (median, 3.5 mg/kg) and the fentanyl 0.5 mcg/kg group (median 3.5 mg/kg) (median differences 1.5, $P$ < .00005, in both comparisons).

**Conclusion** The addition of fentanyl 1 mcg/kg to propofol for brief painful procedures reduces movement, propofol dose, and recovery time. *(J Pediatr 2013;162:137-41)*.

Bone marrow aspiration and lumbar puncture (LP) are brief procedures, but they are associated with pain and anxiety. The repeated need of these procedures during treatment for childhood cancer constitutes a significant burden and the experience is often described as traumatic for patients and their parents.[1] Treatment for pediatric acute lymphoblastic leukemia at our institution requires 15-30 LPs for intrathecal chemotherapy with or without bone marrow aspiration, depending on leukemia risk category; treatment of other diseases also involves frequent painful procedures.

Various pharmacologic regimens have been used to control procedure-related pain in pediatric oncology.[2-5] A recent review of management of painful procedures in children with cancer emphasizes the distinction between sedation and anesthetic regimens and their respective risks and benefits.[6]

Propofol-based total intravenous anesthesia (TIVA) has been studied retrospectively[7,8] and prospectively,[2,9-11] and offers the advantages of rapid onset, titratable level of sedation, rapid recovery, and a good safety profile when administered by trained personnel such as anesthesiologists and pediatric intensivists.[8]

We evaluated 3 propofol-based anesthetic regimens for pediatric oncology procedures using fentanyl 1 mcg/kg, 0.5 mcg/kg, or placebo, and we compared the frequency of postoperative pain and of intraoperative movement and hemodynamic/respiratory instability, the total propofol dose required, and the time to recovery among the 3 groups.

## Methods

St. Jude Children's Research Hospital is a tertiary-care institution for children with cancer and other life-threatening diseases. The facility has multiple outpatient clinics and 60 inpatient beds. Patients range from newborns to young adults at the time of diagnosis.

This prospective study included patients aged 2-17 years who were undergoing treatment for acute lymphoblastic leukemia or lymphoblastic lymphoma and who were expected to undergo at least 3 combined unilateral bone marrow aspiration and LP procedures for intrathecal chemotherapy. Eligible patients were in

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| LP | Lumbar puncture |
| PS | Pain score |
| TIVA | Total intravenous anesthesia |

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complete remission, had a platelet count >50 000/mm$^3$, and had not received daily opioids for pain management during the 2 weeks before the procedures. Patients with neurologic impairment or Down syndrome were excluded, as were patients for whom general anesthesia or any of the anesthetic agents used in the 3 regimens were contraindicated. This study was approved by the St. Jude Institutional Review Board, and written informed consent was obtained from parents or guardians, and assent was obtained from the patients, as appropriate. The trial was registered with ClinicalTrials.gov (NCT00187135).

In a crossover design, each patient was randomly assigned to a schedule that included all 3 treatment regimens in different sequences, and each patient was expected to receive each regimen once. Randomization was stratified by age group (2-4, 5-12, ≥13 years), to ensure that the treatment arms were balanced with respect to age at randomization. A program for conducting randomization was provided by the St. Jude Department of Biostatistics. Study medications were prepared in the pharmacy, labeled "study drug," and delivered to the procedure area. Therefore, clinicians who administered the anesthetics or performed the procedures, the data collection and data analysis teams, and the patients and families were blinded to the assigned regimens. The regimens differed only in the use and dose of fentanyl during induction of anesthesia (1 mcg/kg fentanyl, 0.5 mcg/kg fentanyl, or placebo [normal saline]; treatment arms 1, 2, and 3, respectively). All regimens included topical anesthetic (eutectic mixture of 2.5% lidocaine/prilocaine or 4% liposomal lidocaine) or infiltration of local anesthetic (lidocaine 1%) at the puncture sites and titration of intravenous propofol to immobility and loss of consciousness. All patients reporting pain on waking from anesthesia received 0.5 mcg/kg intravenous fentanyl as needed (maximum 3 doses).

### Description of Monitoring and Anesthetic Technique

Standard monitoring during the anesthetic included intermittent blood pressure measuring, and continuous pulse oximetry, electrocardiogram, respiratory rate, and end tidal carbon dioxide monitoring. Oxygen was administered by face mask for at least 1 minute before the administration of the study drug and continued throughout the anesthetic. Propofol was administered in increments of 1 mg/kg until loss of consciousness, followed by doses of 0.5 mg/kg as needed for any movement during the procedure. Ondansetron was given with the induction of anesthesia as part of the routine clinical care before bone marrow aspiration and LP with intrathecal therapy, to minimize nausea and vomiting.

### Outcome Measures

The primary study outcomes were the frequency of pain (pain score [PS] > 0) and the frequency of severe pain (PS ≥ 5) during recovery from anesthesia. Pain was measured on an 11-point scale, using the Face, Legs, Activity, Cry, Consolability Scale, Faces Pain Scale, or numerical rating system as appropriate for age and cognitive ability.[12-14] Pain was assessed throughout the recovery period (defined as the time from the end of the procedure until an Aldrete score of 8 was reached), and the highest PS during each recovery period was used in comparisons (before administration of fentanyl as needed for pain).

The secondary study outcomes were the frequency of movement during the procedure and the frequency of respiratory or hemodynamic instability (>20% increase in respiratory rate, heart rate, or blood pressure, as indirect measures for inadequate analgesia) during anesthesia. We also compared the time to recovery, the total dose of propofol, and the frequency with which patients required fentanyl for pain during recovery. All the study data were collected by a research associate. All primary and secondary outcome measures were compared across the 3 groups.

### Statistical Analyses

This double-blind, randomized crossover trial was designed with 80% power to detect pairwise differences of 15% in the frequency of post-procedural pain (PS > 0) among the 3 treatment arms with an overall type I error probability of 0.05. The calculated sample sizes needed were 127, 70, and 92 patients for comparison pairs A, B, and C, respectively.

McNemar test was used for pairwise comparisons of the frequency of pain (PS > 0), severe pain (PS ≥ 5), movement, change in vital signs, and fentanyl administration for pain during recovery. The Wilcoxon signed-rank test was used for pairwise comparisons of the median time to recovery and the median total dose of propofol required. In the analysis of the primary outcomes $P$ values of <.0167 were considered statistically significant based on the Bonferroni adjustment for multiple testing to maintain an overall type I error rate of 0.05. $P$ values of <.05 were considered statistically significant for secondary outcomes. All analyses were conducted using the StatXact v. 8 (Cytel Inc, Cambridge, Massachusetts) or SAS v. 9.2 (SAS Institute, Cary, North Carolina) software.

## Results

Between March 2002 and August 2007, 168 patients were enrolled. Six patients withdrew for various reasons before randomization; 162 were randomized and underwent at least 1 anesthetic regimen (**Figure**). Patients' demographic characteristics, diagnoses, and anesthetic regimens are shown in **Table I**. Data from 149 patients (355 procedures) were evaluable for movement and hemodynamic instability. Data from 110 patients (316 procedures) were evaluable for pairwise comparisons of pain during recovery, propofol dose, time to recovery, and use of fentanyl during recovery; 39 patients underwent only one regimen and were excluded from the pairwise comparisons. Regimens 1, 2, and 3 were completed by 111, 129, and 115 patients, respectively. Each patient who underwent at least 2 regimens contributed to the analysis of 3 comparison pairs; 110 and 57 patients completed 2 and 3 regimens, respectively, and comparison pairs A, B, and C included 74, 71, and 79 patients, respectively.