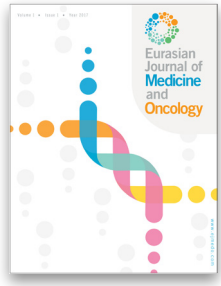
EJMO

DOI: 10.14744/ejmo.2019.70524
EJMO 2019;3(2):120–125



Research Article

The Safety and Efficacy of Propofol Combinations with Ketamine or Fentanyl in Lumbar Puncture Application in Children with Haematological Diseases: A Prospective, Randomised, Single-Blinded Study

Sengul Ozmert,[1] Feyza Sever,[1] Devrim Tanil Kurt,[1] Sibel Saydam,[1] Gulsen Keskin,[1] Yesim Andiran Senayli,[1] Mine Akin,[1] Serap Kirkiz,[2] Nese Yarali[2]

[1]Department of Anaesthesiology and Reanimation, University of Health Sciences Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, Ankara, Turkey
[2]Department of Pediatric Hematology, University of Health Sciences Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, Ankara, Turkey

Abstract

Objectives: The aim of the study was to evaluate reliability, efficiency and side effects of two different combinations that are ketamine-propofol and fentanyl-propofol, in pediatric hematology patients undergoing lumbar puncture (LP).
Methods: A total of 100 paediatric cases, aged 4-14 years, who were planned to undergo LP procedure were administered two different sedo-analgesia protocols. An anesthetist administered ketamine 1 mg/kg intravascularly (iv) to the ketamine group (K), then after 1 min 2 mg/kg propofol was administered iv. In the fentanyl group (F), 1 mcg/kg fentanyl was given and after 1 min 2 mg/kg propofol was administered iv. All patients were monitorized and the heart rate, blood pressure, oxygen saturation, number of LP attempts, the side effects and also additional doses and the physician satisfaction were recorded. (Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital (2015-10)).
Results: The requirement for additional doses was higher in Group F ($p<0.001$) and the physician satisfaction was lower in Group F ($p=0.021$). When hemodynamic parameters were compared, the reduction in F group was determined as greater than that in K group ($p<0.01$).
Conclusion: Safe and effective sedation has been obtained with both protocols during LP. However, the ketamine propofol combination had a lower requirement for additional doses and the physician satisfaction level was higher.
Keywords: Child, fentanyl, ketamine, lumbar puncture, procedural sedation

Cite This Article: *Ozmert S, Sever F, Tanil Kurt D, Saydam S, Keskin G, Andiran Senayli Y, et al. The Safety and Efficacy of Propofol Combinations with Ketamine or Fentanyl in Lumbar Puncture Application in Children with Haematological Diseases: A Prospective, Randomised, Single-Blinded Study. EJMO 2019;3(2):120–125.*

Invasive procedures such as lumbar puncture (LP), bone marrow aspiration and bone marrow biopsy conducted at the diagnosis and treatment stages for children with hematologic diseases have a significant role in modern pediatric hematology. About 50% of children with a hematologic disease may experience pain due to progression, mucositis, chemotherapy and invasive medical procedures.[1]

Performing LP under sedation in pediatric patients reduces the risk of procedure repetition and psychologi-

Address for correspondence: Sengul Ozmert, MD. Saglik Bilimleri Universitesi Ankara Cocuk Sagligi ve Hastaliklari Hematoloji Onkoloji Egitim ve Arastirma Hastanesi, Anesteziyoloji ve Reanimasyon Anabilim Dali, Ankara, Turkey
Phone: +90 532 386 12 01 **E-mail:** sengulozmert@yahoo.com.tr
Submitted Date: November 19, 2018 **Accepted Date:** January 19, 2019 **Available Online Date:** February 22, 2019

cal trauma. The agents used for this purpose should be reliable and short acting, enabling quick recovery, and provide adequate analgesia, amnesia and sedation.[2] Unfortunately, there is no single agent with these characteristics, so anesthetists need to combine various agents.[3]

Various agents in different combinations and doses have been used for invasive procedures in various studies conducted with children with hematologic diseases. However, studies on the combination of propofol with fentanyl and ketamine for intrathecal treatment in the pediatric age group are limited in number. In our study, we used the combination of ketamine providing analgesia, amnesia and loss of consciousness, and fentanyl having strong analgesic characteristics, with propofol in patients undergoing LP. We aimed to compare the reliability, efficiency and side effects of these two different protocols.

Methods

A total of 100 ASA II-III pediatric cases aged 4-14 years who would be undergoing LP for intrathecal treatment at the University of Health Sciences Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital's Hematology Department were included in the study. Two different sedo-analgesia protocols were administered in a randomized, single-blinded and parallel group design after the necessary Ethics Committee permission was obtained. Participants were allocated to two groups by block randomization, with a block size of four. Random Allocation Software Ver. 1.0 was used to create the randomization list. Patients who received fentanyl combined with propofol were called group F, while patients received ketamine combined with propofol were called group K. Both groups consisted of 50 patients. The anesthesist knew which drug combination would be administered while the pediatric hematology resident who performed the LP procedure and the patients did not know it.

Patient with history of allergy to the drugs to be used, soya or eggs; cardiovascular, pulmonary, hepatic, or renal disease; head injury, increased intracranial and intraocular pressure, epilepsy, airway obstruction, facial abnormality, severe obesity, antihistamines and anxiolytic drug use were excluded from the study.

The cases fasted for a minimum of 6 hours before the procedure. The demographic data of the patients were recorded. All cases were administered intravenous (iv) 0.9 % sodium chloride infusion. After the patients were placed in the left lateral decubitus position and were started 6 L min^{-1} O2 via face mask, an anesthetist administered 1 mg kg^{-1} ketamine iv to the ketamine group (Group K). This was followed by 2 mg kg^{-1} propofol iv one minute later. The fentanyl group (Group F) was administered 1 mcg kg^{-1} fentanyl HCl iv. Again, 2 mg kg^{-1} propofol was administered iv one minute later. The administered propofol iv doses were prepared by dilution with SF by half in order to prevent injection pain. The families stayed with their children until they fell asleep. Two minutes after propofol was administered, the physician was allowed to perform the procedure if the Ramsey Sedation Score was 5 or 6.[4–6] If the patient was agitated and moved during the procedure, an additional dose of iv 1 mg kg^{-1} propofol was administered with a slow push. Subsequent additional doses were administered in the same way until satisfactory sedation was obtained. All patients were monitorized and the heart rates, blood pressures, mean arterial pressures, oxygen saturation level of the patients were recorded before induction, at the time of 5 minutes after the ketamine or fentanyl was administered, 5 minutes after the procedure was completed and when leaving the room. Number of LP attempts and the side effects (desaturation, hypersalivation, hypotension, hypertension, bradycardia, injection pain) were recorded. Desaturation was identified as an SPO_2 of <90% or a decrease of more than 10% from the baseline for 1 minute or more, hypersalivation as an excessive amount of saliva draining outside the mouth and/or requiring aspiration to keep the respiratory tract open, hypotension as a decrease of blood pressure by more than 30%, hypertension as an increase of blood pressure by more than 30%, bradycardia as a heart rate <60 min^{-1}, and injection pain as the patient moving and complaining or crying after the administration of propofol. Any minor or major airway problems during the procedure were recorded (a minor airway problem was identified as problem that could be improved with manual manipulation and a major airway problem as a problem requiring the use of an ambu or intubation). The number of additional doses of propofol, the duration from the administration of the ketamine or fentanyl until the withdrawal of the spinal needle (the drug-procedure duration) and the duration from the withdrawal of the needle at the end of the successful LP procedure until the time of arriving at level IV criteria for being sent back to the patient bed (recovery duration), and the satisfaction of the pediatric hematology resident performing the procedure (very satisfied/satisfied/not satisfied) were recorded. The criteria for the patient being sent back to the patient bed from the procedure room were as follows: (I) The presence of airway control that will provide adequate oxygenation, (II) being awake or easily awakened, (III) presence of the swallowing reflex, (IV) regaining the pre-sedation responses.[7] The patients who reached level IV after the procedure were taken to the recovery unit and monitorized with continued O_2 administration.

Outpatient were sent home after similar observation at the recovery unit for 1 hour after the procedure. The patients who were hospitalized or sent home were asked whether they saw nightmares after the first 24 hours and whether they had headaches after the 1st and 5th days at the bedside or with a telephone call respectively.

Statistical Analysis

Total amount of propofol requirements to be administered in addition to the anesthetic substances fentanyl and ketamine in our study into account and assuming an alpha of 0.005, power of 0.80 and effect size of 0.65 the necessary minimum sample size as calculated as 39 children for each group (G*Power 3.1.9.2.).[8]

All data were evaluated by using IBM SPSS Statistics for Windows ver. 23 software (IBM Corp., Armonk, NY). Chi-square test and Fisher's exact test were used to compare categorical variables between Fentanly and Ketamine groups. Independent samples t test and Mann-Whitney U test were used to compare normally and non-normally distributed continuous variables, respectively. Two-way repeated measure ANOVA was also used to evaluate time, group and group*time interaction effect for hemodynamic parameters. Statistical significant level was accepted as 0.05.

Results

No statistically significant differences were obtained between the two groups for age, gender, weight, ASA score, diagnosis, drug-procedure duration, recovery duration (duration between the withdrawal of the needle at the end of the successful LP procedure and time when the patients were lucid), and number of LP attempts (Table 1).

Comparison of the heart rate, and the systolic, diastolic and mean blood pressure by time revealed that, the decrease in F group was more prominent than in the K group ($p<0.01$). Evaluation of the hemodynamic data 5 minutes after the drug was administered, 5 minutes after the procedure, and when leaving the room showed higher values in the K group than the F group ($p<0.01$). Hemodynamic values during lumbar puncture were significantly higher in the K group than the F group ($p<0.001$) (Fig. 1).

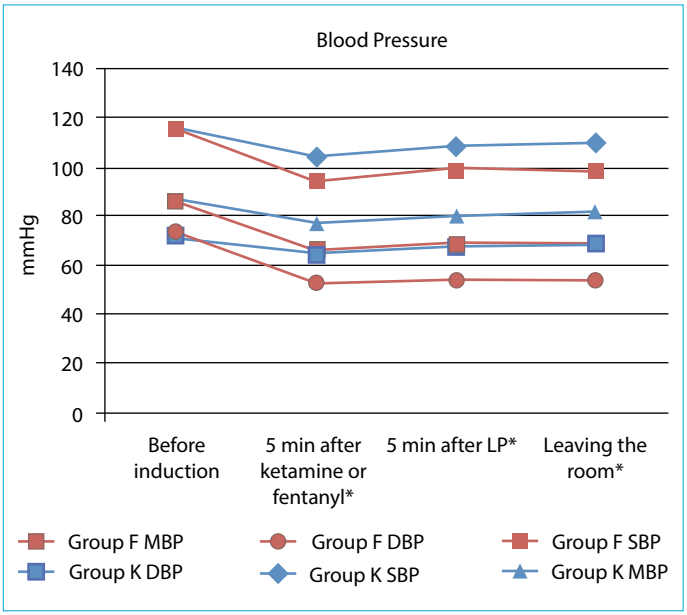


Figure 1. Change of hemodynamic variables in time according to groups.

*Evaluation of the hemodynamic data 5 minutes after the drug was administered, 5 minutes after the procedure, and when leaving the room showed higher values in the K group than the F group ($p<0.01$).

Table 1. Comparing and processing of demographic data and recovery period

	Fentanyl (n=50)	Ketamine (n=50)	p
Age	8.6±2.8	8.8±2.9	0.910
Gender, F/M	14/36	15/35	0.826
Weight	29.9±9.8	31±9.5	0.686
Diagnosis			
ALL/AML/AA	48/1/1	46/3/1	0.385
ASA II/III	0/50	2/48	0.153
Number of LP attempts	1.4±1.2 (min=1, max=8)	1.4±0.7 (min=1, max=4)	0.149
Drug-procedure duration (min)	8.0±3.5	8.5± 2.2	0.096
Recovery time (min)	5.1± 2.1	5.5± 2.2	0.593
Pediatric hematologist satisfication			
Very satisfied/satisfied/not satisfied	39/11/0	47/3/0	0.021

Values are presented as mean±SD and patients number; ALL: Acute lymphocytic leukemia; AML: Acute myelocytic leulemia; AA: Aplastic anemia.

A statistically significant difference was found regarding the need for additional doses and pediatric hematology resident satisfaction. The need for additional doses was higher in the F group (p=0.007) and pediatric hematology resident satisfaction was lower in the F group (p=0.021) (Table 1, 2).

No statistically significant difference was found between the two groups in terms of side effects and airway problems over the entire duration of the procedure (p>0.05). The drug was administered through the peripheral vascular route in 26% of the F group and 24% of the K group subjects and through the central venous route in the other patients (p>0.05). Injection pain was only evaluated in patients with an peripheric venous access route. There was no pain in any patient with central access. No significant difference was found between the groups regarding the symptoms 24 hours after the procedure (Table 3). No difference was found between the two groups for oxygen saturation (p>0.05).

Table 2. Propofol (1 mg/kg) additional doses amount

Additional doses	Fentanyl (n=50, %)	Ketamine (n=50, %)	p
0	26 (52)	44 (88)	
1	18 (36)	5 (10)	
2	3 (6)	1 (2)	0.007
3	1 (2)		
4	1 (2)		
6	1 (2)		

Values are presented as patients number.

Table 3. Side effects and complains in first 24 hours

	Fentanyl (n=50)	Ketamine (n=50)
Side effects		
Hypotension	5	2
Hypertension	-	1
Hypersalivation	-	3
İnjection pain	1	-
Bradycardia	2	-
Desaturation	-	-
Major airway problem	-	-
Minor airway problem	1	5
Complains in first 24 hours		
No	47	45
Headhache	3	3
Headhache+Nightmare	-	2

Values are presented as patients number.

Discussion

General anesthesia or analgesia with combination of sedative drugs has been recommended for painful procedures in pediatric oncology by the American Academy of Pediatrics (AAP) and the World Health Organization (WHO).[9–11] We used two different sedo-analgesia protocols consisting of the combination of propofol, a hypnotic sedative agent, with fentanyl or ketamine, and aimed to investigate which combination was safer and more effective. We chose patients scheduled to undergo LP due to hematologic disease to ensure homogeneity in our study. An additional dose of propofol was required in 24 patients in the F group and 6 patients in the K group in our study. The number of LP attempts was higher in patients needing a larger number of additional doses (>2). The pediatricians conducting the procedure were less satisfied in the F group but the difference was not statistically significant. A similar study compared groups that received propofol and ketamine or propofol and alfentanil and the need for additional propofol was less in the ketamine group.[6] These results show that the ketamine-propofol combination provides more effective sedation. The authors did not find a significant difference between the groups despite a longer time to awakening in the group administered ketamine.[6] Tian and his friends found the longest recovey period to be 5 minutes in their studies which had the subject of children who were diagnosed with leukemia and who were administered fentanyl propofol combination for sedation.[12] In our study, there is no difference with regard to recovery time which is 5.1 minutes for the group F and 5.5 minutes for group K.

Changes in heart rate, systolic, diastolic and mean blood pressure recorded from the administration of the ketamine or fentanyl to the time the patient left the room were compared between the two groups, the decrease in group F was more than in group K (p<0.01). This is thought to be related to the balancing of propofol's CVS-depressing effect by ketamin's sympathomimetic effect, maintaining hemodynamic stability.[13] Our results also support this opinion. Another study comparing pediatric oncology patients receiving propofol or midazolam/ketamine for procedural sedation reported similar results with a significant decrease in all CVS parameters of the propofol group.[14] In the study Crea et al.[6] conducted, heart rate and respiratory rate were significantly lower in propofol-alfentanil group.

We did not administer anticholinergic agent with ketamine and there was not much hypersalivation as expected in our patients. Hypersalivation was noted in 3 of 50 patients in the K group but no patient in the F group. Hypersalivation was reported in 1 of 25 patients administered midazolam/ketamine without anticholinergic by Gottschling et al.[14] The

O_2 saturation did not decrease in the patient with hypersalivation and an anticholinergic agent was not required. Another study on the use of ketofol for sedation in children with hematologic disease did not report hypersalivation in any of the patients although the number of patients was only 20.[7] We believe that performing the procedure in the lateral position with O_2 support, prevented the airway obstruction and desaturation that could develop due to the hypersalivation.

When compared with the use of propofol by itself, the propofol-fentanyl combination decreases the total propofol dose and its side effects.[5, 15] The most important concern with ketamine use is nightmare and hallucinations.[2] On the other hand, the side effects decrease when used with propofol.[16, 17] None of our patients had a major airway problem requiring a breathing apparatus (ambulation) or intubation. Although minor airway problems requiring cranial extantion and jaw elevation occurred in 1 patient in the F group and 5 patients in the K group, manual manipulation was enough to resolve the problem in a few seconds. All patients were administered 6 L min^{-1} oxygen with a mask, preventing desaturation development. Gottschling et al.[14] reported desaturation in 9 patients in the propofol group and 3 patients in the ketamine + midazolam group but it improved spontaneously within a few seconds or by administering O_2 with a mask, none of the patients requiring ambu use or intubation. In another retrospective study, there were no statistically significant differences between the groups in terms of side effects (desaturation, apnea, hypotension, bradycardia, etc.) caused by deep sedation in pediatric patients undergo LP alone and combined procedure (LP and KIA). Also in the same study they have found the incidence of serious side effects (emergent airway intervention, cardiac arrest atc) to be much higher for the group undergo combined procedure.[18] We believe that administration of O_2 during the procedure increases safety.

We diluted 1% propofol 1:1 with physiological saline to prevent propofol-related injection pain. The drugs were administered through the peripheral vascular route in 13 of the 50 patients in the F group and in 12 patients in the K group and injection pain occurred in only one patient in the F group. Gottschling et al.[14] reported that injection pain occurred in 5 of 25 patients in the propofol group that received propofol diluted 1:1 with physiological saline. Our results are consistent with the literature. We believe that the dilution of propofol with physiological saline is useful for the prevention of injection pain and also provides an opportunity for a slow and soft induction.

Post-spinal headache incidence has been reported at a rate of 8-14 % in relevant studies.[19, 20] We asked the patients or the relatives whether they had suffered nightmares or headaches, 24 hours after the LP procedure in our study. Only one patient stated experiencing a fearful dream after the administration of ketamine for sedation at two different times. The rate of seeing nightmares was 4%. This patient was found to suffer simultaneous headache. Headache was seen in 8 (8%) patients in our study. Our results are again consistent with the literature. We believe the low rate of nightmares in our study is due to the combination of ke-tamine with propofol.[21] The rate of seeing nightmares was reported as 3.3% in a study where only ketamine was used for sedation during painful oncology procedures in 119 pediatric patients.[22]

We did not follow-up nausea and vomiting as our patient group was routinely administered antiemetics both before and after intrathecal treatment. We could have standard-ized the procedure by having the same physician to per-form all lumbar punctures but this was unfortunately not possible due to routine clinic duties.

Conclusion

In conclusion, fast induction and recovery was provided to-gether with safe and efficient sedation using two different protocols consisting of the combination of ketamine and fentanyl with propofol during LP for treatment and diag-nosis. We recommend ketamine and propofol combination for LP instead of fentanyl and propofol combination as it requires fewer additional doses, is satisfactory for the prac-titioners and provides safe and efficient sedation.

Disclosures

Ethics Committee Approval: Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital (2015-10). All procedures performed in stud-ies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.O., F.S.; Design – S.O.; Supervision – S.O., F.S.; Materials – S.O., F.S.; Data collection &/or processing – S.O., F.S., D.T.K., S.S., G.K., Y.S.A., M.A., S.K.; Analysis and/or interpretation – S.O., F.S.; Literature search – S.O., F.S., N.Y.; Writing – S.O., F.S.; Critical review – S.O.

References

1. Alexander J. Manno M. Underuse of analgesia in very young patients with isolated painful injures. Ann Emerg Med 2003;41:617–22. [CrossRef]
2. Loh G, Dalen D. Low-dose ketamine in addition to propofol for procedural sedation and analgesia in the emergency depart-

ment. Ann Pharmacother 2007;41:485–92. [CrossRef]
3. Arora S. Combining ketamine and propofol ("ketofol") for emergency department procedural sedation and analgesia: a review. West J Emerg Med 2008;9:20–3.
4. Ramsay MA, Savage TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J 1974;2:656–9.
5. Hollman GA, Schultz MM, Eickhoff JC, Christenson DK. Propofol-fentanyl versus propofol alone for lumbar puncture sedation in children with acute hematologic malignancies: propofol dosing and adverse events. Pediatr Crit Care Med 2008;9:616–22. [CrossRef]
6. Crea F, Ruggiero A, Genovese O, Tortorolo L, Zorzi G, Chiaretti A. Safety and efficacy of two protocols for sedation in pediatric oncology procedures. Cent Eur J Med 2008;3:77–82.
7. da Silva PS, de Aguiar VE, Waisberg DR, Passos RM, Park MV. Use of Ketofol for procedural sedation and analgesia in children with hematological dieases. Pediatr Int 2011;53:62–7.
8. Ghadami Yazdi A, Ayatollahi V, Hashemi A, Behdad Sh, Ghadami Yazdi E. Effect of two Different Concentrations of Propofol and Ketamine Combinations (Ketofol) in Pediatric Patients under Lumbar Puncture or Bone Marrow Aspiration. Iran J Ped Hematol Oncol 2013;3:187–92.
9. Zelter LK, Altman A, Cohen D, LeBaron S, Munuksela EL, Schechter NL. American Academy of Pediatrics Report of the Subcommittee on the Management of Pain Associated with Procedures in Children with Cancer. Pediatrics. 1990;86:286–31.
10. Gray A. Book review: Cancer pain relief and palliative care in children WHO Publication, Geneva 1998. Ann Saudi Med 1999;19:388–9. [CrossRef]
11. Coté CJ, Wilson S; American Academy of Pediatrics; American Academy of Pediatric Dentistry; Work Group on Sedation. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. Pediatrics 2006;118:2587–602.
12. Tian X, Yang YH, Wei H, Lao JQ, Wang HP, Tian YY. Rapid sedation induced by fentanyl combined with propofol via an intrathecal chemotherapy injection for leukemia in children. Genetics and Molecular Research 2015;14:3687–93. [CrossRef]
13. Botero CA, Smith CE, Holbrook C, Chavez AM, Snow NJ, Hagen JF, et al. Total intravenous anesthesia with a propofol-ketamine combination during coronary artery surgery. J Cardioyhorac Vas Anesth 2000;14:409–15. [CrossRef]
14. Gottschling S, Meyer S, Krenn T, Reinhard H, Lothschuetz D, Nunold H, et al. Propofol versus midazolam/ketamine for procedural sedation in pediatric oncology. J Pediatr Hematol Oncol 2005;27:471–6. [CrossRef]
15. Disma N, Astuto M, Rizzo G, Rosano G, Naso P, Aprile G, et al. Propofol sedation with fentanyl or midazolam during oesophagogastroduodenoscopy in children. Eur J Anaesthesiol 2005;22:848–52. [CrossRef]
16. Guit JB, Koning HM, Coster ML, Niemeijer RP, Mackie DP. Ketamine as analgesic for total intravenous anaesthesia with propofol. Anaesthesia 1991;46:24–7. [CrossRef]
17. Butterworth IV JF, Mackey DC, Wasnick JD. Intravenous Anesthetics. Clinical Anesthesiology. 5th edition. New York: Mc Graw Hill; 2013. p. 182.
18. Patel MM, Kamat PP, McCracken CE, Simon HK. Complications of deep sedation for individual procedures (lumbar pucture alone) versus combined procedures (lumbar puncture and bone marrow aspirate) in pediatric oncology patients. Hosp Pediatr 2016;6:95–102. [CrossRef]
19. Keidan I, Bieloreia B, Berkenstadt H, Aizenkraft A, Harel R, Huna-Baron R, et al. Prospective evaluation of clinical and laboratory effects of intrathecal chemotherapy on children with acute leukemia. J Pediatr Hematol Oncol 2005;27:307–10.
20. Ramamoorthy C, Geidusechek JM, Bratton SL, Miser AW, Miser JS. Postdural puncture headache in pediatric oncology patients. Clinical Pediatrics 1998;37:247–52. [CrossRef]
21. Messenger DW, Murray HE, Dungey PE, van Vlymen J, Sivilotti ML. Subdissociative-dose ketamine versus fentanyl for analgesia during propofol procedural sedation: A randomized clinical trial. Acad Emerg Med 2008;15:877–86. [CrossRef]
22. Evans D, Trunham L, Barbour K, Kobe J, Wilson L, Vandebeek C, et al. Intravenous ketamine sedation for painful oncology procedures. Pediatr Anesth 2005;15:131–8. [CrossRef]