Cent. Eur. J. Med. • 3(1) • 2008 • 77-82
DOI: 10.2478/s11536-008-0001-6

VERSITA

Central European Journal of **Medicine**

Safety and efficacy of two protocols for sedation in pediatric oncology procedures

Research article

Francesca Crea[1*], Antonio Ruggiero[2], Orazio Genovese[1], Luca Tortorolo[1], Giulia Zorzi[1], Antonio Chiaretti[1]

[1] *Pediatric Intensive Care Unit, Catholic University Medical School, Rome, Italy*

[2] *Department of Pediatric Oncology, Catholic University Medical School, Rome, Italy*

Received 11 July 2007; Accepted 25 November 2007

Abstract: Invasive procedures, such as the lumbar puncture, can cause anxiety and pain in children undergoing treatment for acute lymphoblastic leukemia (ALL). We investigated the safety and efficacy of two different protocols for pain relief in 20 children with ALL undergoing lumbar puncture. Protocol A was composed of an association between propofol and alfentanil. Protocol B consisted in the combination of propofol and ketamine. Vital and behavioural parameters, sedation and pain scores were recorded at different times during and after the procedure. All patients showed a satisfactory sedation and analgesia. We found a statistically significant difference of vital parameters between protocol A and protocol B, while there were no significative differences between sedation scores and the other parameters evaluated. Patients in protocol A showed a higher incidence of major side effects, such as respiratory depression. Our results show that both protocols are effective to obtain a good sedation and analgesia in children with ALL undergoing lumbar puncture, but the association between propofol and ketamine appears more safe due to the lower incidence of side effects.

Keywords: *Childhood • Lumbar Puncture • Oncology • Pain • Sedation*

1. Introduction

About 50% of children with cancer experience pain as a result of the tumor progression, mucositis, chemotherapic treatment or needle medical procedures. Despite the effective drugs for pain relief and the detrimental effects cancer pain can have on the child's health status, it is often inadequately assessed and treated [1,2]. Sedative-hypnotics and opioids are the most common drugs for pain relief in children with cancer who experience moderate or severe pain due to the medical procedures and/or the tumor progression [3-6]. These drugs require to be safe, short-acting and effective in order to obtain an adequate analgo-sedation outside the operating-room, where the painful procedures are often carried out. Up to date, many compounds, such as propofol, alfentanil, remifentanil, and ketamine have been assessed to provide analgesia and sedation in children [7,8]. Propofol is an ultra-short acting sedative agent with rapid onset, substantial potency, extremely short recovery, and high satisfaction to patients due to its antiemetic and euphoric properties. However, when used alone a relatively large dose may be required to provide satisfactory comfort and such high doses may be responsible of cardiovascular and respiratory depression [9,10]. Alfentanil is a synthetic opioid, chemically related to fentanyl, with a rapid onset and short elimination half-life used for short time pediatric painful procedures, such as bone marrow aspiration [11,12]. Ketamine is a short-acting analgesic drug that has been extensively used for pediatric procedures in and out of the operating room and appears to be the preferred agent for parents and physicians. It provides effective analgesia and sedation with a low incidence of side effects [13]. A recent review (Munro 2007) showed efficacy and safety profile of ketamine and midazolam[14]. Nevertheless, not many trials have been performed in children to assess what drugs, or combination of these, should be considered

* *E-mail: francescacrea@email.it*

as safe and effective for an adequate pain relief during painful procedures, such as the lumbar puncture. Lumbar puncture is one of the most common painful procedures that children with acute lymphoblastic leukemia (ALL) undergo and generally local anesthesia is not sufficient to prevent pain. Based on those clinical aspects of pain, the aims of our study were to compare safety and efficacy of two different protocols for pain relief in children with ALL undergoing a therapeutic lumbar puncture outside the operating-room.

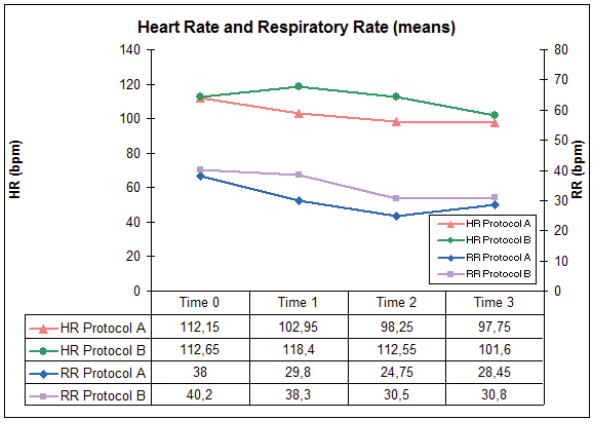
2. Material and Methods

From January 2006 to September 2006 we have conducted a prospective, cross-over study in children with ALL, which required analgesia and sedation for the execution of lumbar puncture, to evaluate the safety and efficacy of two different protocols (protocol A and protocol B) for pain relief during this procedure. All the sedations were performed in the emergency department by pediatric intensivists or anaesthesiologist. To minimize any bias due to the individual responses to the administered drugs, both of the protocols were administered to all patients enrolled in the study, according to the cross-over method. Protocol A was composed of a starting dose of propofol (2 mg/kg), followed from a single dose of alfentanil (20 µg/kg). Protocol B consisted in a starting dose of propofol (2 mg/kg), followed from a single dose of ketamine (1 mg/kg). If sedation was inadequate (i.e. if the patient's level of sedation was not sufficient to allow execution of the lumbar puncture) patients received a repeated dose of sedative agent (propofol 1 mg/kg), in order to compare how the analgesic drug (alfentanil or ketamine) influenced the number of propofol boluses throughout the procedure. All drugs were administered as an intravenous bolus in one minute. All patients had a central venous catheter for delivering sedative and analgesic drugs during the procedure. Lumbar puncture was performed two minutes later the administration of the analgesic drug. According with ASA score (wich describes the physical status o patients) we excluded all the subjects with impaired clinical status (ASA score > 4) [15]. Patients were not eligible for the study if they were ASA 4 grade, were suffering from central apnea or respiratory failure, cystic fibrosis, renal failure, liver diseases, endocranial hypertension, and hemodynamic or cardiac dysfunction. Safety and depth of sedation of the single protocol was evaluated by monitoring vital parameters, such as heart rate (HR), respiratory rate (RR), and pulse oximetry (O_2Sat), at different times during the procedure: T_0 before sedation started, T_1 immediately after the administration of propofol and analgesic drug, T_2 as the oncologist was performing the spinal puncture, T_3 5 minutes later the end of the procedure. At these times were checked closely also the drug's side effects, such as bradycardia, hypotension, hypoxia, apnea, nausea and vomiting. Bradycardia was defined as a HR lower than the 3rd percentile for the age, hypotension as a blood pressure lower than the 3rd percentile for the age, and hypoxia as a $SatO_2$ < 92% at room air. If bradycardia or bradypnea occurred, the sedation was stopped, patient was aroused from sleep and, if necessary, atropine was administered. If patient experienced hypoxia in room air, O_2 was administered by facial mask until $SatO_2$ >95% was recovered. The efficacy of the single protocol was evaluated using Ramsay and CHEOPS scales (Children's Hospital of Eastern Ontario Pain Scale), depending on the patients' age and general clinical conditions, and with a questionnaire administered to the children at the time of awaking in order to assess patients' compliance and satisfaction [16,17]. Time to awakening was determined by measuring the time between the initial administration of drugs and the time that patients opening their eyes and talked. Ramsay scale is a suitable way of evaluating the depth of the sedation's state after drug's infusion and during the sedation. On the other hand, CHEOPS scale was administered at the moment of the awakening and it is useful to evaluate intensity of post-procedural pain. Other parameters considered for the evaluation of the efficacy of two protocols were immobilization's degree and number of attempt required to perform lumbar puncture, time and quality of the awaking after each protocol, time to discharge from the sedation's room, time to which the child was permitted to take something by mouth, and, finally, time to discharge from the ward or Day-Hospital rooms. Moreover, all children older than 3 years were requested to complete a questionnaire of their grade of satisfaction before and after the procedure in order to evaluate the previous experience of painful procedures and the satisfaction degree of the current analgesia. The Ethical Committee of the hospital approved the study and the parents of all patients involved provided written informed consent.

2.1. Statistical analysis

Data are reported as mean ± standard deviation (DS). Statistical analyses were performed with PSS ver 13.0 for Windows. Vital parameters such as HR, RR and O_2Sat were analyzed using two-tailed t test. Kolmogorov-Smirnov test was applied to establish if these data showed normal distribution. All of the remaining parameters were analyzed using Wilcoxon's ranked sum test. Adverse effects were analyzed using Fischer's exact test. We considered $p < 0.05$ to indicate statistical significance.

Figure 1. Heart rate (HR) and respiratory rate (RR) variations during drug administration. At time T_0 starting values of HR were similar in both the groups without any statistical difference (p=0.9). At time T_1 and T_2 HR decreased significantly in protocol A respect to protocol B (p=0.009 and p=0.008, respectively). No differences were noted during the remaining time of observation. RR also showed a significantly greater reduction in protocol A respect to protocol B at time T_1 and T_2 (p=0.03). No differences were found during the remaining time of observation.

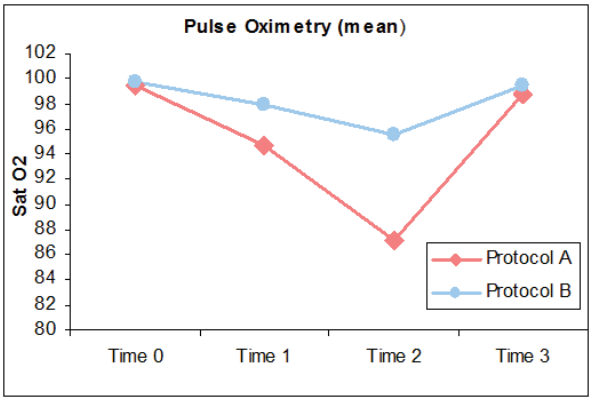


	Time 0	Time 1	Time 2	Time 3
HR Protocol A	112,15	102,95	98,25	97,75
HR Protocol B	112,65	118,4	112,55	101,6
RR Protocol A	38	29,8	24,75	28,45
RR Protocol B	40,2	38,3	30,5	30,8

3. Results

Twenty patients with low-risk ALL undergoing a therapeutic lumbar puncture were enrolled in the study. The age of these patients ranged from 2 to 15 years (median 7.3± quartile ranges: 5,75/8,25). All patients experienced analgo-sedation with both protocols in according to the cross-over method. In all, the procedures counted 40 lumbar punctures, 20 for each protocol. All patients were in the maintaining phase of therapy and were receiving chemotherapy for their consolidation treatment which consisted of intravenous high-dose-metrotrexate, intrathecal methotrexate, and oral 6-mercaptopurine. In Figure 1 we report the variations of vital parameters recorded during the procedures when sedation was obtained using propofol plus alfentanil (protocol A) or propofol plus ketamine (protocol B). The figure shows a statistically significant difference of HR and RR values between protocol A and protocol B at time T_1 and T_2. Regarding the O_2Sat evaluation, alfentanil brought significantly on deeper O_2Sat reduction at time T_2 compared to ketamine (p=0.02), while no significant differences were found among the other times (Figure 2). Nine children belonging to alfentanil group who had experienced respiratory depression required supplemental oxygen by facial mask, even thought neither transient bag-valve-mask ventilation or endotracheal intubation were necessary. In particular, oxygen desaturation events occurred in 11 out of 20

Figure 2. O_2Sat variations during drug administration. Protocol A caused a significantly deeper O_2Sat reduction at time T_2 respect to protocol B (87% versus 95%, respectively). (p=0.02). No significant statistically differences were found among the other time.



children who received alfentanil (protocol A) and only in 3 out 20 in those ones who received ketamine (protocol B). In all patients satisfactory sedation was obtained and there was no statistical difference between sedation scores of the two groups during and after the painful procedure. In particular, in the protocol A CHEOPS score means was 5.25 ± 0.6, while in the protocol B CHEOPS score means was 5.5 ± 0.5 (p>0.05). Ramsay score means was 6.08 ± 1.2 in the protocol A vs 6.15 ± 1.1 in the protocol B, respectively (p>0.05). The number of attempt requested to perform lumbar puncture was only one for both protocols. The mean of time to awakening was 20.72 ± 10.7 minutes in protocol A and 25.85 ± 13.1 minutes in protocol B. Time to discharge from sedation's room was about 30 minutes for both protocols. Time to which children were permitted to take something by mouth was 130.2 ± 45.2 minutes in protocol A and 134.4 ± 25.9 minutes in protocol B. Time to discharge from the ward or Day-Hospital rooms was 182.3 ± 45.2 minutes in protocol A and 184.5 ± 38.9 in protocol B. All these parameters did not show any statistical difference between the two protocols. Sedation efficacy was also assessed as immobilization's degree and as need of additional propofol's boluses to obtain an adequate analgesia during the lumbar puncture. In this regard, both children who received alfentanil as part of sedation schedule, and those ones whom ketamine was administered to, required some supplemental bolus of propofol (1 mg/kg). Overall number of propofol's boluses was of 15 in the alfentanil group (protocol A) and only 5 in the ketamine's one (protocol B). We have also analyzed the answers to the questionnaire that was filled in by children older than 3 years. After the awakening no children reported that they had felt pain during the procedure. Ninety per cent of children

in protocol A had felt pleasant sensations when they awoke, and 3 children in protocol B reported dreaming pleasantly. All of children sedated with ketamine were not afraid at the moment of awakening while the 20% of children belonging to alfentanil group felt little fear. Regarding the minor side effects related to the drugs utilized, one child each protocol showed rash and 2 children belonging to the ketamine group complained of nausea and diplopia when they awoke, respectively.

4. Discussion

Intrathecal prophylaxis by lumbar puncture plays a central rule in the management of haematological and oncologic disorders in children as well. As lumbar puncture causes a moderate to severe pain and anxiety, an adequate analgesia and sedation is required when the procedure is planned. Our study shows that both protocols utilised proved to be effective in prompting an appropriate degree of sedation and analgesia during the procedure. All enrolled children showed a satisfactory grade of immobilization that ensured to perform the lumbar puncture on first attempt and to collect the liquoral samples without any difficulty. All patients showed a long standing hemodynamic stability with some important differences between the two protocols. In protocol A (propofol plus alfentanil) statistically significant differences were noted regarding the HR, RR, and O_2Sat values, as compared to protocol B (propofol plus ketamine). Propofol was used in both protocols because of his safety and efficacy, as demonstrated in several studies [18-20]. These differences were more evident at time T_1 and T_2, probably related to the extremely rapid effects of alfentanil on the cardio-respiratory system. The greater number of apnoeas and oxygen desaturation events in this group had required oxygen supplementation by facial mask for about 50% of these, even thought neither bag-valve-mask ventilation or endotracheal intubation were necessary. Respiratory depression observed in protocol A may be due to the bond between alfentanil and type μ opioid receptors, that are responsible for both the pharmacological and early side effects (time T_1 and T_2 of our study). So, physicians should take into account this potential adverse effect when they plan to perform procedural sedation outside the operating room by using alfentanil. Recently, the use of alfentanil in pediatric procedural sedation has been evaluated by several studies. Antmen et al. investigated the efficacy and safety of alfentanil alone, or in association with midazolam, in providing analgo-sedation in children who underwent a diagnostic bone marrow aspiration, stating that both of these schedule are effective [11]. Our results are in keeping with this study, confirming that the use of alfentanil, in association with propofol, is safe and effective for pain relief in children with ALL, even if a particular attention must be taken on its important side effects. On the other hand, the most frequent adverse reaction related to ketamine are hallucinations and occur more commonly when this drug is administered alone. Moreover, it has been known that combination of ketamine with propofol reduces this unfavorable effect [19]. Our study confirms these data as only 3 out of 20 patients reported on their own dreams during sedation with propofol and ketamine. In addition, post-anesthetic agitation and hallucinations associated with the use of ketamine, as well as diplopia and nystagmus, are much less frequent after propofol anesthesia. In the experts' opinion, the combination of these drugs is the most effective and safety scheme in the pediatric and neonatal procedural sedation due to their synergistic effect and to the stability of hemodynamic parameters of their concurrent administration [20,21]. Our results are consistent with those findings because the number of additional propofol boluses, needed to obtain an adequate analgo-sedation during the lumbar puncture, was lower when propofol was administered in association with ketamine (protocol B) respect to protocol A (propofol plus alfentanil). Efficacy of administered drugs was also confirmed by assessing the behavioral parameters, such as CHEOPS and Ramsay scales. During and after the execution of the lumbar puncture both scores showed a satisfactory degree of sedation and analgesia, without any significant difference between the two protocols. Nevertheless, statistically significant differences were noted neither in the time to awakening nor in sedation's length. Children were early discharged from the sedation's room and could be in their own beds after 30 minutes since the ending of the procedure and could speak with their parents or watch television. They were, moreover, permitted to eat after about two hours to lumbar puncture, obtaining a very good degree of satisfaction, especially for younger children. Time to discharge from the ward or Day-Hospital rooms was of about 3 hours since the ending of the sedation with both protocols. The optimal timing of discharge from the sedation room after pediatric procedural sedation has not been yet well established. A recent study stated that serious adverse effects such as hypoxia, stridor or hypotension, rarely occurred after 25 minutes from the drugs administration [22]. Our results are in keeping with this study, confirming that discharge from the sedation room may be safe at approximately 30 minutes after the end of sedation as no side effects were reported by the children or their parents during this observational time. Short timing of hospitalization represents a significant

advantage of procedural sedation performed outside the operating-room, since children spend little time in the hospital without any alterations in their own ordinary life. The safety of ketamine protocol make it possible to perform analgesia procedures also in treatment room outside ER, in presence of skilled physicians and cardiorespiratory monitoring About the answers to the questionnaire all children did not show any forewarned fear, anxiety or apprehension at the time of the following procedure, demonstrating the good degree of amnesia too. Moreover, all patients stated that they had not feel any pain, irrespective of the administered drugs, confirming further the good degree of analgesia.

In conclusion, despite some limitations (low number sample and not randomized controlled clinical trial) it seems that our data show that the using of a sedative drug, such as propofol, in association with an analgesic one, such as alfentanil or ketamine, is safe and effective schedule to obtain a good procedural sedation and analgesia in children with ALL undergoing lumbar puncture. Both of the protocols are effective, but the association between propofol and ketamine results in a more safe schedule due to the lower incidence of side effects respect to the combination between propofol and alfentanil.

References

[1] Alexander J., Manno M., Underuse of analgesia in very young patients with isolated painful injures, Ann Emerg Med, 2003, 4, 617-622

[2] Yeh C.H, Lin C.F., Tsai J.L., Lai Y.M., Ku H.C., Determinants of parental decisions on drop out from cancer treatment for childhood cancer patients. J Adv Nurs, 1999, 30, 193-199

[3] Anderson C.T.M., Zeltzer L.K., Fanurik D.,Procedural pain, in: Schechter NL, Berde CB, Yaster M (ed): Pain in infants, children and adolescents. Baltimore: Williams and Wilkins", 1993

[4] Keidan I., Berkenstadt H., Sidi A., Perel A. Propofol/ remifentanil versus propofol alone for bone marrow aspiration in paediatric haemato-oncological patients, Paediatr Anaesth, 2001, 11, 297-301

[5] Krauss B., Green S.M., Sedation and analgesia for procedures in children, N Eng J Med, 2000, 342, 938-945

[6] Litman R.S., Conscious sedation with remifentanil and midazolam during brief painful procedures in children, J Pain Simptom Manage, 2000, 19, 468-471

[7] Foubert L., Reyntjens K., Wolf D., Suys B., Moerman A., Mortier E., Remifentanil infusion for cardiac catheterization in children with congenital heart disease, Acta Anaesthesiol Scand, 2002, 46, 355-360

[8] Hostetler M.A., Auinger P., Szilagyi P.G., Parenteral analgesic and sedative use among ED patients in the United States: combined results from the National Hospitalal Ambulatory Medical Care Survey (NHAMCS) 1992-1997, Am J Emerg Med, 2002, 20, 139-143

[9] Green S.M., Krauss B., Profol in emergency medicine: pushing the sedation frontier, Ann Emerg Med,2003, 42, 773-782

[10] Wehrmann T., Kokabpick S., Lembcke B., Caspary W.F., Seifert H., Efficacy and safety of intravenous propofol sedation during routine ERCP: a prospective, controlled study, Gastrointest Endosc, 1999, 49, 677-683

[11] Antmen B., Sasmaz I., Birbicer H., Ozbek H., Burguts R., Isik G., et al, Safe and effective sedation and analgesia for bone marrow aspiration procedures in children with alfentanil, remifentanil and combination with midazolam, Pediatric Anesthesia, 2005, 15, 214-219

[12] Bailey P.L., Stanley T.H., Intravenous opioid anesthetics, in: Stoelting RK, Miller RD (ed): Basics of anesthesia, 4rd ed., New York N, Churchill Livingstone, 1994

[13] Kim G., Green S.M., Denmark T.K., Krauss B., Ventilatory response during dissociative sedation in children: a pilot study, Acad Emerg Med, 2003, 10, 140-145

[14] Munro A., Machonochie I., Midazolam or ketamine for procedural sedation of children in the emeregency department, Emerg Med J, 2007, 24, 579-580

[15] Walker R, ASA and Cepod scoring, Update in anaesthesia, 2002, 14, 1

[16] Crellin D., Sullivan T., Babe F., Analysis of the validation of existing behavioral pain and distress scales for use in the procedural setting Pediatr Anesthesia, 2007, 17, 720-733

[17] Carrer S., Bocchi A., Candini M., Donegà L., Tartari S., Short term analgesia based sedation in the Intensive Care Unit: morphine vs remifentanil and morphine, Minerva Anestesiol Vol, 2007, 73, 327-332

[18] Kaabachi O., Chettaoui O., Ouezini R., Abdelaziz AB, Cherif R, Kokki H, A ketamine-propofol admixture does not reduce the pain on injection compared with a lidocaine-propofol admixture, Pediatr Anaesthes, 2007, 17, 734-737

[19] Guit J.B., Koning H.M., Coster M.L., Niemeijer R.P., Mackie D.P., Ketamine as analgesic for

total intravenous anaesthesia with propofol, Anaesthesia, 1991, 46, 24-27

[20] Golden S., Combination propofol-ketamine anaesthesia in sick neonates, Paed Anaesth, 2001, 11, 119-122

[21] Ostreikov I.F.,. Milenin V.V, Vasil'ev IaI, Mishustin V.V., Cherdantsev S.V., Central hemodynamics conditions of combined intravenous anesthesia using propofol and ketamine in pediatric ophthalmology, Anesteziol Reanimatol, 2002, 11, 22-24

[22] Newman D.H., Azer M.M., Pitetti R.D., Singh S., When is a patient safe for discharge after procedural sedation? The timing of adverse effect events in 1367 pediatric procedural sedations, Ann Emerg Med, 2003, 42, 627-635