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Comparison of the Analgesic and Sedative Effects of Midazolam-Ketamine and Propofol-Sufentanil Combinations in Painful Procedures of Children with Haematologic Malignancy

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Abstract

Objective: Bone marrow aspiration and lumbar puncture play essential roles in the diagnosis and treatment of haematological disorders. These repeated invasive procedures lead to considerable pain and stress in children, which is emotionally stressful for their parents. This study aimed to compare the effectiveness and outcomes of two combinations of midazolam-ketamine (MK) and propofol-sufentanil (PS) in painful procedures of children with haematologic malignancy.

Methods: In this prospective, randomised, double-blind clinical trial, we enrolled 80 eligible patients with haematologic malignancy aged 2–14 years. We randomly allocated them to the MK and PS groups. We recorded and compared the level of sedation, pain severity, hemodynamic indices, the onset of effect, duration of recovery and complications during and after procedure in the two groups. We analysed the data using the SPSS software. We used Mann–Whitney U, independent t-test, chi-square and Fisher's exact tests to compare continuous and categorical variables.

Results: From initially enrolled patients, 68 patients completed the study (38 in PS and 30 in MK group). The levels of sedation and the mean score of pain intensity were significantly lower in the MK group than those in the PS group ($p<0.05$). Movements and the needs to repeat the dose were significantly lower in the MK group than those in the PS group ($p<0.05$).

Conclusion: During bone marrow aspiration and lumbar puncture procedures in children with haematologic malignancy, the findings of this trial suggest that MK combination therapy provides better sedation and analgesia than PS.

Keywords: Haematologic malignancy, ketamine, midazolam, propofol, sufentanil

Introduction

Bone marrow aspiration (BMA) and lumbar puncture are the most common invasive procedures in the management of paediatric haematology and oncology diseases (1). These procedures are painful and consequently cause a great deal of anxiety for these children and their families (2, 3). Since these measures are frequently repeated during their diagnosis or treatment process (4), proper sedative methods are needed to prevent pain, excessive motion and anxiety during the procedures (1). Different techniques to reduce pain, including effective education for parents, preparation of the patient for the procedure, cognitive behavioural therapy, sedation and general anaesthesia, have been reported in this regard (4).

Different pharmacological agents have been introduced, and their effectiveness has been evaluated. An appropriate pharmacological agent should have a rapid onset of action, short duration of activity and easily adjustable level of

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sedation. It should also provide stable cardiorespiratory function during procedure (1).

Propofol is a sedative agent with a rapid onset and end of effect. In spite of appropriate sedative property, it is associated with dose-dependent respiratory depression, hypotension and no intrinsic analgesic property. It is recommended to use propofol with another analgesic agent, such as an opiate, during painful procedures to decrease the required dosage of both of these drugs. The risk of respiratory depression is high for propofol (5, 6).

Ketamine is an analgesic as well as sedative agent that could be used alone or with other drugs to induce analgesia during diagnostic and therapeutic procedures in children (6, 7). It is considered as a safe and effective anaesthetic with a few limitations including delayed awakening, use in emergencies, nausea and vomiting. The risk of hypertension and increased heart rate is high for ketamine because of its sympathetic stimulation effect (5, 8).

Opioid agonists such as fentanyl, alfentanil and remifentanil are commonly used potent analgesics that could provide rapid onset and relatively short duration. All mentioned properties are useful during anaesthetic induction, the injection of local anaesthetic and the stimulating portions of the surgery. The short clinical half-lives of these opioids are particularly beneficial for ambulatory anaesthesia (9).

Based on the available evidence, a specific agent with above-mentioned properties has not yet been introduced; and there is no standard protocol in this field. So, that combination therapy has been introduced to achieve these goals (8). The World Health Organisation and the American Academy of Paediatrics (AAP) (10) have also proposed it. Some studies have evaluated some combination therapies in this field (11-13).

Main Points:

- Although the time of interval until awakening and the duration of recovery were shorter in the PS than those in the MK group, the difference was not statistically significant.
- This study showed that MK and PS combinations provide effective sedation and analgesia during painful procedures in haematologic malignancy.
- But some properties of MK combination including the wide margin of safety of ketamine dose and the absence of cardiopulmonary suppressive property, as well as the anxiolytic and analgesic effects in children, make the MK combination more favorable than PS.
- During the procedure, the frequency of patients' movement was significantly higher in the PS that in the MK group, but two groups had no significant difference in receiving extra dosage of the drugs.
- The recovery time is less with PS, and there are fewer side effects during the recovery period.

Some studies have evaluated the combination of propofol with fentanyl or remifentanil. Some studies have investigated the effectiveness of MK in the procedures and reported appropriate outcomes for this combination (11-14). The sedative and analgesic effects of PS combination have not been studied in this group of patients and children. But available date suggested that it could provide appropriate analgesic and sedative effects (15, 16).

So far, no studies have compared the sedative and analgesic effects of two combinations of MK and PS in children with haematologic malignancy undergoing BMA or lumbar puncture. Thus, this study aimed to compare the effectiveness and outcomes of the two combinations regarding pain control and appropriate sedative condition during the procedure in children with haematologic malignancy undergone painful procedures.

Methods

This prospective, randomised, double-blind clinical trial was carried out in the paediatric oncology-haematology ward of Omid Hospital, affiliated to Isfahan University of Medical Sciences, Iran, in 2017.

The regional ethics committee of Isfahan University of Medical Sciences reviewed and approved the protocol of this study (Ethic ID: IR.MUI.REC.1396.3.441). The trial was registered in the Iranian Registry of Clinical Trials with a registration ID of IRCT20170809035601N8.

In this study, 124 patients aged 2-14 years who were scheduled for elective painful diagnostic procedures including bone marrow biopsy (BMB) or BMA were included. Excluding criteria were history of recent head injury, neurological abnormality, cardiopulmonary disease, drug allergies, using sedative or analgesic drugs before the study or having acute pain syndrome. We obtained informed consent from all patients and/or their parents in accordance with the Declaration of Helsinki. The study schedule is shown in Figure 1.

Priori power analysis indicated that we needed to have 40 subjects in each groups to have 80% power for detecting a medium-sized effect of 26% in desired level of sedation when employing 0.05 criterion of statistical significance.

We randomly allocated the selected patients into two groups using a computerised random number generator: midazolam-ketamine (MK) and propofol-sufentanil (PS) (17).

Table 1. The University of Michigan Sedation Scale (UMSS)

Value	Patient state
0	Awake and alert
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated: deep sleep, aroused only with significant physical stimulation
4	Unarousable

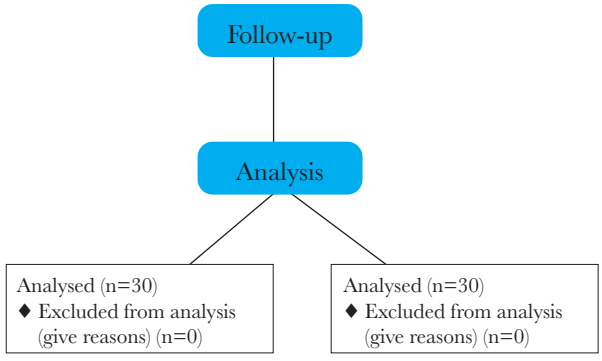

Figure 1. Consort flow diagram of the study

In the operating room, all patients were monitored by electrocardiography (ECG), pulse oximeter and automated non-invasive arterial pressure. During procedure and in recovery room, all patients received oxygen supplementation by nasal cannula (2 L min^{-1}). Airway management equipment was bedside of patients.

An anaesthesiologist who was not involved in data collection prepared study drugs in four syringes, containing propofol 0.75 mg kg^{-1}, sufentanil 0.5 µg kg^{-1} for the propofol-sufentanil (PS) group; and midazolam 0.04 mg kg^{-1}, ketamine 0.75 mg kg^{-1} for the MK group. After covering with aluminium foil, all syringes were coded for blinding. The anaesthesiologist and operation room personnel were unaware about the nature of the drug to be used for the patients. All the codes remained closed until the study was finished. The study drugs were given slowly over 1 min.

A spontaneous eyelid closure with a level of sedation that provides safe execution of the procedure with no visible pain was considered the clinical sedation endpoint.

After achieved to adequate sedation level, a paediatric haematologist performed the procedures.

During the procedure, for cases with inadequate sedation level, additional boluses of sedative agents, MK or PS, were administered with 2-min intervals.

The level of the patients' sedation, the quality of pain relief, heart rate (HR), mean arterial pressure (MAP), systolic (SBP) and diastolic blood pressure (DBP) and blood oxygen saturation were checked by the blinded observer every 5 min during the procedure and in the recovery room every 10 min. The sedation level of studied patients were scaled using the University of Michigan Sedation Scale (UMSS) (Table 1).Value of 2 or 3 is considered as the appropriate level of sedation before and during procedure (18).

The Universal Pain Assessment Tool (UPAT) is scaled from 0 to 10 with the following scores: no pain with 0, mild pain with 1-2, moderate pain with 3-4 and 5-6 and severe pain with score more than 6. The patients who achieved an Alderete score of 9 were considered for being discharged from the recovery.

Statistical analysis

Data were analysed using IBM Statistical Package for the Social Sciences (IBM SPSS Corp.; Armonk, NY, USA) version 23. Normality of the data distribution was studied for each variable (Shapiro-Wilk test, $p<0.05$). All data were confirmed to have normal distribution except for pain intensity. We used the Mann-Whitney U test, independent t-test, chi-square and Fisher's exact tests to compare continuous and categorical variables. P value less than 0.05 was considered as the significant level for all the statistical tests.

Results

In this study, 124 eligible patients with haematologic malignancy were enrolled. Based on inclusion criteria, 80 patients were assigned into two equal groups (40 in the MK group and 40 in the PS group). In the MK group (n=38) and in PS group (n=30), patients received allocated drug combinations. The analysis consisting of 47 males and 21 females underwent procedural sedation and analgesia for BMA/BMB.

Demographic characteristics and frequency of different procedures in studied children in the MK and PS groups are presented in Table 2. No significant difference was observed between both groups regarding their sex, age and body weight ($p>0.05$).

Table 2. Demographic characteristics and frequency of different procedures in children with haematologic malignancy in the midazolam-ketamine (MK) and propofol-sufentanil (PS) groups

Variables	MK group n=38	PS group n=30	Statistical test	p
Female/Male [n (%)]	11 (28.9%)/27 (71.1%)	10 (33.3)/20 (66.7%)	Chi-square test	0.69
Age (years)*	6.71 (3.71)	6.73 (3.28)	Independent t-test	0.97
Weight (kg)*	21.16 (10.32)	22.57 (11.86)	Independent t-test	0.60
Procedures				
Intrathecal (IT)	19 (50%)	12 (40%)	Chi-square test	0.49
Bone marrow aspiration (BMA)	5 (13.2%)	8 (26.7%)		
Bone marrow biopsy (BMB)	7 (18.4%)	7 (23.3%)		
BMA/BMB	6 (15.8%)	3 (10%)		
*Mean(SD)				

Table 3. Frequency of different level of sedation, pain intensity and timing of the procedures in children with haematologic malignancy in the midazolam-ketamine (MK) and propofol-sufentanil (PS) groups

Variables	MK group n=38	PS group n=30	p
Level of sedation			
Level of sedation by UMSS [n (%)]			
2	1 (2.6%)	26 (86.6%)	<0.001
3	29 (82.8%)	4 (13.3%)	
4	8 (21%)	0 (0%)	
Pain intensity			
Level of pain intensity by UPAT [n (%)]			
None	2 (5.3%)	0 (0%)	0.04
Mild	30 (78.9%)	18 (60%)	
Moderate	6 (15.8%)	12 (40%)	
Timings of the procedure (min)*			
Onset of effectiveness	4.92 (1.30)	2.57 (0.85)	<0.001
Duration of the procedure	4.74 (0.95)	5.00 (1.39)	0.35
Time interval from the end of the procedure until patient's awakening	9.16 (7.85)	5.53 (4.03)	0.02
Recovery duration	45.47 (8.49)	41.33 (12.43)	0.10
*Mean(SD)			

Frequency of different type of procedures had no significant difference in studied groups (p>0.05). Frequency of different level of sedation, pain intensity and timing of the procedures in children with haematologic malignancy in MK and PS groups are presented in Table 3. At the beginning of the study, level of sedation in the two studied groups was not significantly different; but in the MK group had significantly better quality of sedation than the PS group (p<0.05). Frequency of higher scores of pain was significantly higher in the PS group (p<0.05).

The mean of onset of effectiveness time was significantly shorter in the MK group (p<0.05). No significant difference was observed between two groups regarding the duration of the procedure and the duration of recovery (p>0.05). The mean interval time from the end of the procedure until patient's awakening was significantly shorter in the PS group (p<0.05). Mean (SD) of hemodynamic variables before, during and after procedure are presented in Table 4. The mean hemodynamic variables were not different between groups before procedure (p>0.05). The mean SBP, DBP and MAP were significantly lower in the PS group than those in the MK group during and after procedure (p<0.05).

Frequency of movement during the procedure was significantly higher in PS group than that in the MK group (56.7% vs. 28.9%, p=0.021).

In the MK group and the PS group, 15.8% and 33.3% of the patients required extra doses of the drug, respectively (p=0.090).

Discussion

This study evaluated sedative and analgesic effects of the MK and PS combinations during lumbar puncture and BMA in

Table 4. Mean (SD) of hemodynamic variables before, during and after procedures in children with haematologic malignancy in the midazolam-ketamine (MK) and propofol-sufentanil (PS) groups

Variables		MK group n=38	PS group n=30	p
HR (per min)	Before procedure	107.47 (17.26)	106.57 (24.25)	0.85
	During procedure	106.58 (14.95)	99.70 (17.77)	0.08
	After procedure	103.97 (16.40)	99.33 (19.80)	0.29
SPO (percent)	Before procedure	97.95 (1.335)	98.00 (1.33)	0.87
	During procedure	99.58 (0.64)	99.43 (1.87)	0.65
	After procedure	99.37 (0.97)	99.33 (0.95)	0.88
SBP (mmHg)	Before procedure	118.50 (27.80)	109.67 (11.55)	0.10
	During procedure	117.47 (15.94)	97.57 (13.49)	0.00
	After procedure	107.63 (15.43)	95.03 (13.31)	<0.001
DBP (mmHg)	Before procedure	76.50 (15.71)	72.50 (14.81)	0.28
	During procedure	79.50 (14.46)	59.20 (16.32)	<0.001
	After procedure	68.26 (15.26)	55.77 (11.13)	<0.001
MAP (mmHg)	Before procedure	92.95 (15.81)	85.83 (15.04)	0.06
	During procedure	95.42 (14.87)	73.90 (14.40)	<0.001
	After procedure	84.84 (15.54)	72.07 (11.86)	<0.001

HR: heart rate; SPO_2: oxygen saturation; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure

children with haematologic malignancy. Our findings indicated that regarding sedation and pain relief, the MK group was superior to the PS group.

In terms of hemodynamic indices, though during and after procedure mean SPB, DPB and MAP were significantly lower in the PS than those in the MK group, both groups were in stable condition. During the procedure, the frequency of patients' movement was significantly higher in the PS than that in the MK group, but two groups had no significant difference in receiving extra dosage of the drugs.

Although the time of interval until awakening and the duration of recovery were shorter in the PS than those in the MK group, the difference was not statistically significant. In the study by Pellier and colleagues, they concluded that midazolam with ketamine provides an effective and safe combination for pain control in patients with paediatric oncology. Accordingly, their combination could efficiently induce brief unconscious sedation in accordance with analgesia (14). Akbulut et al. (19) evaluated the combinations of MK and propofol-fentanyl (PF) during upper gastrointestinal endoscopy in children, both combinations induced effective sedation, MK accompanied more comfortable. In the MK group, the level of sedation during the intervention was significantly higher than that in the PF group. On the other hand, in the PF group, recovery period was shorter, and they experienced fewer complications during the recovery period. The results of this study were in accordance with the mentioned study. Godambe et al. (20) compared the combination of FP with MK during orthopaedic procedures in the emergency wards. In this study, the total duration of sedation in the FP group was significantly shorter than that in the MK group. Recovery time was also longer in the MK group than that in the FP group. FP was comparable to MK in reducing discomfort associated with painful orthopaedic procedures in the paediatric emergency wards. Our findings regarding the shorter period of sedation and recovery in the PS group than that in the MK group was similar to the above-mentioned study, but the appropriate quality of sedation and analgesia in the MK group than PS group in our study was not similar to their results.

Considering the importance of sedation and analgesia during BMA and BMB in children with haematologic malignancy, in previous studies, various drug combinations have been evaluated with the aim of finding an effective and safe combination (21, 22).

The effectiveness of the MK combination has been reported in various clinical conditions. In rhinoplasty, combination of MK with a dose of 0.1 mg kg^{-1} for midazolam and 0.5 mg kg^{-1} for ketamine has been reported to be more effective and preferable than midazolam only (23).The combination can be effectively used for sedative and analgesic use. Nevertheless, combinations of ketamine-midazolam (KM) can be considered with a lower risk of hypoxemia and lower pain score as a logical combination for orthopaedic interventions in the emergency department (24). Kennedy et al. (25) demonstrat-

ed that KM combination is safer and more effective than fentanyl-midazolam in orthopaedic procedures, because of higher pain anxiety scores in the fentanyl-midazolam group. Jamal et al. (26) reported lower pain score during procedure for KM than for the MF group but similar procedure success rate and pain score during reduction for the groups.

Different studies have evaluated the combinations of propofol with different opioids. Though the effectiveness of propofol and fentanyl or remifentanil have been evaluated in some studies (11, 12), a few studies have evaluated the sedative and analgesic effects of PS combination. Sufentanyl is more potent than fentanyl.

Shetabi et al. (13) evaluated the combinations of propofol-ketamine with propofol-remifentanil during BMA or BMB and LP in children with acute lymphoblastic leukaemia (ALL). Both combinations induced effective sedation, but the combination of propofol-ketamine was more appropriate for children with ALL especially in patients with unstable hemodynamic. In a study that was conducted on 100 children aged 2-14 years who were referred for short-term surgical procedures, the effectiveness of the two drug combinations of ketamine-propofol and sufentanil-propofol were compared. The study showed that the combination of ketamine-propofol would cause a better sedation and analgesia, resulting hypotension and apnoea were lower with this combination compared to the other. This combination was preferred in terms of hemodynamic stability (5). Ramalinga et al. (27) indicated that in short-term painful procedures like BMA/BMB particularly in children and elderly patient, an appropriate choice would be general anaesthesia using propofol and fentanyl.

The limitations of this study were the lack of comparisons between the different doses of drugs combination, limited sample size and the objective evaluation of the level of sedation in patients. It is recommended to design further studies with consideration of mentioned limitations.

Conclusion

This study showed that MK and PS combinations provide effective sedation and analgesia during painful procedures in haematologic malignancy. But some properties of MK combination including the wide margin of safety of ketamine dose and the absence of cardiopulmonary suppressive property, as well as the anxiolytic and analgesic effects in children, make the MK combination more favourable than PS. The recovery time is less with PS, and there are fewer side effects during the recovery period. It seems that in MK combination, the rapidly reversible association of ketamine and midazolam, effective analgesic effect, the modality for use in painful outpatient procedures of any type and number as well as minimal morbidity and feasibility at any age make it a proper combination therapy to achieve a qualified anaesthesia during painful procedures in children with haematologic malignancy.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Isfahan University (Ethic ID: IR.MUI.REC.1396.3.441).

Informed Consent: Written informed consent was obtained from all patients and/or their parents who participated in this study.

Peer-review: Externally peer-reviewed.

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