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INDONESIAN JOURNAL OF ANESTHESIOLOGY AND REANIMATION
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Original Article

KETAMINE VERSUS TRAMADOL EFFECTIVENESS AS POSTOPERATIVE ORAL ANALGESICS ON PEDIATRIC PATIENTS AGE 5-10 YEARS IN ELECTIVE SURGERY AT DR. SOETOMO HOSPITAL SURABAYA

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ABSTRACT

Introduction: The use of ketamine and tramadol as postoperative analgesics for pediatric are still relatively rare, especially orally administrated. As an analgesic, ketamine blocks the NMDA receptor, the main excitatory transmitter in CNS; whereas tramadol blocks serotonin and norepinephrine uptake, thus preventing pain transmission on the spinal cord. **Objective:** The aim of this study is to compare the effectiveness of oral ketamine and oral tramadol as analgesics for postoperative acute pain in children. **Method:** A double-blind randomized clinical trial was conducted at Dr. Soetomo Hospital. The hospital ethical committee had approved this study. The subject includes thirty children aged 5-10 years old who fulfilled the inclusion criteria. They were divided into either ketamine groups or the tramadol group, in which each group consisting of fifteen patients. The regimen dosage that been given was 2mg/kg tramadol and ketamine as postoperative oral analgesics in the form of simple syrup. The FLACC table was used to evaluate pain score before and after administration of drugs (30-minutes, 1-hour, 2-hours, 3-hours, 4-hours, and at discharge from the recovery room). **Result and Discussion:** Based on the quantitative parameter of the FLACC (scale 0-10), there was a significant difference ($p<0.05$) between the first-hour postoperative administration and patient discharge from the recovery room. The patient of ketamine group had far lower FLACC value compared to the tramadol group. Rescue analgesics in the form of intravenous fentanyl were given to one patient (6.7%) in the ketamine group and four patients (26.7%) in the tramadol group. **Conclusion:** Ketamine proved to be a better and more effective postoperative oral analgesic compared to tramadol in this study.

Keywords: Ketamine; Oral Analgesic; Pediatric; Postoperative Pain; Tramadol

ABSTRAK

Pendahuluan: Penggunaan ketamine dan tramadol sebagai analgesik pasca operasi untuk pediatrik masih relatif jarang, terutama pemberian secara oral. Sebagai analgesik, ketamine bekerja dengan menghambat reseptor NMDA, pemancar rangsang utama dalam SSP; Sedangkan tramadol bekerja dengan menghambat penyerapan serotonin dan norepinefrin, sehingga menghambat nyeri di sumsum tulang belakang. **Tujuan:** Tujuan dari studi ini adalah untuk membandingkan efektivitas oral ketamine dan tramadol sebagai analgesik untuk nyeri akut pasca operasi pada pasien anak. Metode yang digunakan adalah studi *double-blind randomized clinical trial* dilakukan di rumah sakit Dr. Soetomo. Studi ini telah disetujui oleh komite etika rumah sakit. Sampel studi berjumlah tiga puluh anak berusia 5-10 tahun setelah kriteria inklusi. Mereka dibagi menjadi salah satu kelompok ketamin atau kelompok tramadol, yang masing-masing kelompok yang terdiri dari lima belas pasien. Dosis obat yang diberikan adalah 2mg/kg baik tramadol maupun ketamine sebagai analgesik oral pasca operasi dalam bentuk sirup sederhana. Tabel FLACC digunakan untuk mengevaluasi nyeri sebelum dan sesudah pemberian obat (30-menit, 1 jam, 2-jam, 3-jam, 4-jam, dan pada saat keluar dari ruang pemulihan). **Hasil dan Pembahasan:** Berdasarkan parameter kuantitatif dari FLACC (skala 0-10), perbedaan yang signifikan ($p < 0.05$) ditemukan antara jam pertama setelah pemberian obat dan saat pasien dari keluar dari ruang pemulihan. Pasien dalam kelompok ketamin memiliki nilai FLACC jauh lebih rendah dibandingkan dengan kelompok tramadol. Obat analgesik dalam bentuk fentanyl intravena diberikan kepada satu pasien (6,7%) dalam kelompok ketamin dan empat pasien (26,7%)

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dalam kelompok tramadol. **Kesimpulan:** Ketamin terbukti lebih baik dan lebih efektif sebagai analgesik oral pasca operasi dibandingkan dengan tramadol dalam studi ini.

Kata kunci: Ketamin; Analgetik Oral; Pediatric; Nyeri Paska Operasi; Tramadol

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INTRODUCTION

Acute pain, in general, is considered as an unpleasant stimulus and experience in children's population as result from postoperative, their illness, wound, or medical procedures that need to be done. Fourty percents of pediatric surgical patients, from a survey from 20 years ago, experienced moderate or severe postoperative pain and 75% of them had insufficient analgesia. (1) Pain in children is usually under treatment because of some reasons: worries the risk of opioid (respiratory depression) and the unproven safety and efficacy of the analgesics. A dogma suggested that the children do not feel pain, it is dangerous giving powerful analgesia in children and it will cause the children on the risk of addiction. (2) In highly developed health care system countries, several studies conducted that even in the first decade of the 21st century, postoperative pain for children was not managed well in most of the patients. For example, an epidemiological study in the Czech Republic (2006), 18.5% of patients complained about pain to be the worst experience in postoperative and 36% of them complained after surgery. In 2014, the study was repeated at the same place (the results in 2006 have not been published yet) and revealed that less than 20% of patients suffered from severe pain, none of them reported excruciating pain and 6 hours after surgery the incidence of severe pain fell below 10% (3). In Indonesia, there is still no specific study about postoperative pain in children.

The selection of analgesics and the role of administration, especially for young children, which give the most beneficial regarding the effectiveness and continuance, are still to be examined further. Therefore, this study is subjected to find the efficacy of the oral drug in treating postoperative pain in children. Ketamine and Tramadol are analgesics that often used for the treatment of postoperative pain in adult patients (4)(5). Usage in children as postoperative oral analgesics, especially on per-oral route is still rare (6).

Ketamine is a chemically stable non-opioid drug with analgesic effect at low doses (7). Ketamine gives analgesia by antagonism of the N-Methyl-D-Aspartate (NMDA) receptor in the Central Nervous System (CNS). Intravenous (IV) ketamine can provide postoperative analgesia in many clinical trials, especially to reduce opioid consumption. However, IV administration has limitations, such as ketamine is considered as an anesthetic drug and should be administered in the monitored location. Therefore, using oral ketamine for the management of acute pain for postoperative surgery or after trauma is highly desirable (7). In research conducted by Saied et. Al showed that oral ketamine at a dose of 1-2 mg kg-1 administrated in 8-hour period, can be effective analgesics not that occurrence of emergence (8)(9).

Tramadol is a medium potency analgesic drug. Tramadol is a unique drug because of its two mechanisms of action. First, its metabolites have a weak affinity for mu-opioid receptors and no affinity for delta or kappa receptors. The second mechanism is the

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ability to inhibit the reuptake of the norepinephrine and serotonin neurotransmitters. Tramadol provides less sedation compared to other opioids with minimal effects on respiration, which is an advantage over another opioid and can be used for postoperative pain relief in children. A study for oral tramadol in children showed a dose-ranging effect, with patients receiving 2 mg kg-1 dose, requiring 42% less rescue analgesia than patients who received 1 mg kg-1 dose (10). Tramadol also has a different advantage because of its lack of inhibition on prostaglandin synthesis over NSAIDs. Oral tramadol has the same analgesic efficacy as oral sodium diclofenac for 11 years and older patients post-tonsillectomy pain, without the side effects of NSAIDs (10). It is best used as an analgesic supplement to treat mild to moderate pain because of its opioid-sparing effect and low incidence of side effects.

The author has conducted preliminary research on the use of both drugs intravenously. The research is in collaboration with Kanudjoso Djatiwibowo Hospital in Balikpapan and Interplast Australia-New Zealand. It was held in May 2012, from 84 patients with congenital lip cleft abnormalities (> 6 months) undergoing surgery and administered ketamine and tramadol intravenously 10 minutes before surgery was completed, only 3.57% (3 people) were guided (emergence) after the operation in the recovery room and 2.38% (2 people) who experienced vomiting after surgery so that requires additional therapy in the ward.

Therefore, this study is subjected to compare the effectiveness of oral ketamine and oral tramadol as analgesics for acute postoperative pain in children. The subject in this study were children aged 5-10 years old who underwent surgery with moderate to severe pain levels. Children age 5-10 years old can express pain response more accurately, and also can memorize well, so if postoperative pain is not be handled well, it will impact their psychological development. Drugs choice for this study are chosen because ketamine and tramadol have a good analgesic effect, easy to get and cheap; also given orally to reduce the children's fear of injection.

MATERIAL AND METHOD

This double-blinded clinical trial was conducted in 2014 on 30 children aged 5-10 years old who were referred to Dr. Soetomo Hospital in Surabaya. Inclusion criteria were: being aged 5-10 years old, meeting ASA I or II criteria and candidate for elective surgery with general anesthesia. Exclusion criteria were: children who had organ failure, septic, increased intracranial pressure (ICP), history of using MAO inhibitor drugs, neuroleptics or other sedative, seizures, and they who need fasting after surgery. The ethics committee of the Dr. Soetomo Hospital approved this study. After informed consent was obtained from the parents, patients who met inclusion criteria were divided randomly into two groups: group A (ketamine 2 mg kg-1 orally) and group B (tramadol 2 mg kg-1 orally). Hospital pharmacist, who was not involved in patient management, made both study drugs into simple syrup coded bottle A and B with the same dosage 10 mg ml-1 and given to the patients by responsible anesthetists who were blinded study group allocations. Before premedication was given, the pain scale was recorded with FLACC (Table 1) and WBFS (Figure 1). Midazolam 0.05-0.1 mg kg-1 and Atropine Sulphate 0.01 mg kg-1 intravenous were used as premedication. General anesthesia was induced with fentanyl 2 μg kg-1 followed by propofol 2 mg kg-1 and atracurium 0.5 mg kg-1. Morphine 0.05-0.1

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mg kg-1 intravenous was given as analgesia during surgery, maintenance with Isoflurane, and O2. If the surgery was more than 3 hours, additional fentanyl 0.5 - 1µg kg-1 can be administered when necessary. Standard monitoring was used throughout anesthesia. 30 minutes before surgery was ended, NSAID 10 mg kg-1 intravenous was given.

In recovery room patients were given drug A or B according to randomization. After that, FLACC and WBFS were used to score the pain intensity in 30-minutes, 1-hour, 2-hours, 3-hours, 4-hours, and when the patients were discharged from the recovery room. If the patients experienced severe pain, they were given the following analgesics according to the pain measurement: NSAID 15 mg kg-1 iv for FLACC 4-6 or WBFS 2-3; and fentanyl 0.1 µg kg-1 iv for FLACC 7-10 or WBFS 4-5.

Side effects such as emergence, nausea, and vomiting were recorded after the intervention. If the patients were emergence, midazolam 0.1 mg kg-1 was given. If nausea and vomiting occurred, metoclopramide 0.1 mg kg-1 iv and dexamethasone 0.1 mg kg-1 iv were given.

Power calculation had indicated that 15 children would be required per group to detect a difference of FLACC and WBFS with a power of 84% and $\alpha = 0.05$. SPSS 12 software was used for data analysis. To compare two groups, a T-two free sample test was used. A P-value less than 0.05 was considered as a significant level.

Table 1. FLACC (Face, Legs, Activity, Consolability) Scale

Category	Scoring		
	0	1	2
Face	*No particular expression or smile*	*Occasional grimace or frown, withdrawn disinterested*	*Frequent to constant quivering chin, clenched jaw*
Legs activity	*Normal position or relaxed*	*Uneasy, restless, tense*	*Kicking or legs were drawn up*
Cry	*No cry (awake or asleep)*	*Moans or whimpers; occasional complaint*	*Crying steadily, screams or sobs, frequent*
Consolability	*Content, relaxed*	*Reassured by occasional touching, hugging or being talked to distractible*	*Difficult to console or comfort*

Figure 1. Wong-Baker Faces Pain Scale

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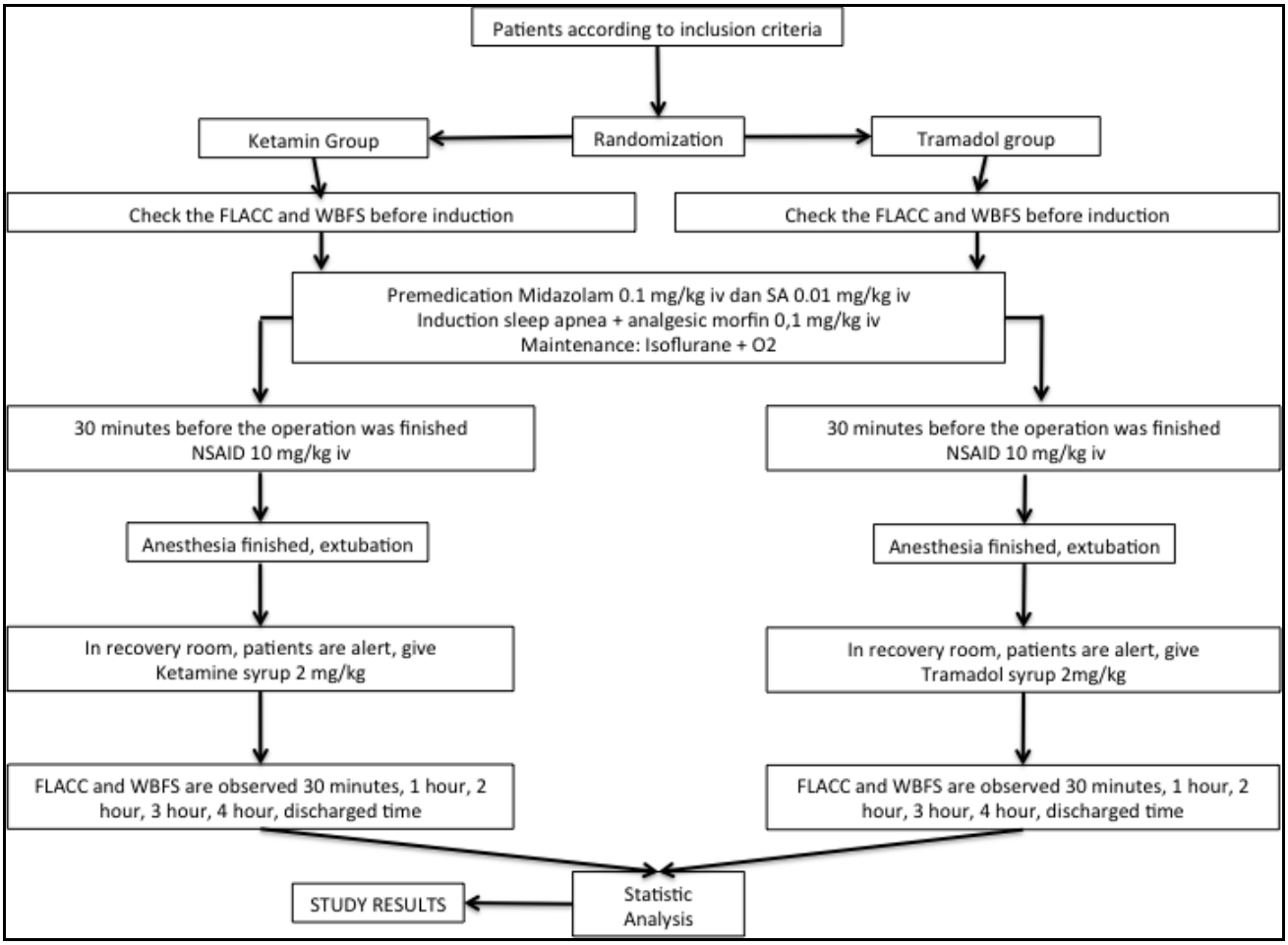

Figure 2. Method scheme

RESULT AND DISCUSSION

There were no significant differences among the groups for sex distribution, age, body weight, height, ASA status, and duration of surgery (Table 2).

A Significant difference was found starting from 1-hour post-intervention until the patients discharged from the recovery room. FLACC score in the ketamine group was significantly lower than the tramadol group ($p = 0.04$) (Figure 3), while there was no significant difference in WBFS score (Figures 4 and 5). In pain assessment with the WBFS parameter at 2-hour post-intervention cannot be analyzed statistically due to homogeneous samples (all samples included in no-pain scale).

Table 2. Comparison of demographic characteristic between groups

	Group A Ketamine	Group B Tramadol
Age	7.73±1.86	7.26±1.79
Sex (Female / Male)	9 / 6	6 / 9
Weight (kg)	26.73±11.34	25.93±10.29
Height (cm)	118.80±18.46	113.8±13.18
ASA status (I / II)	7 / 8	9 / 6
Duration of surgery (h)	2.36±1.61	2.63±1.49

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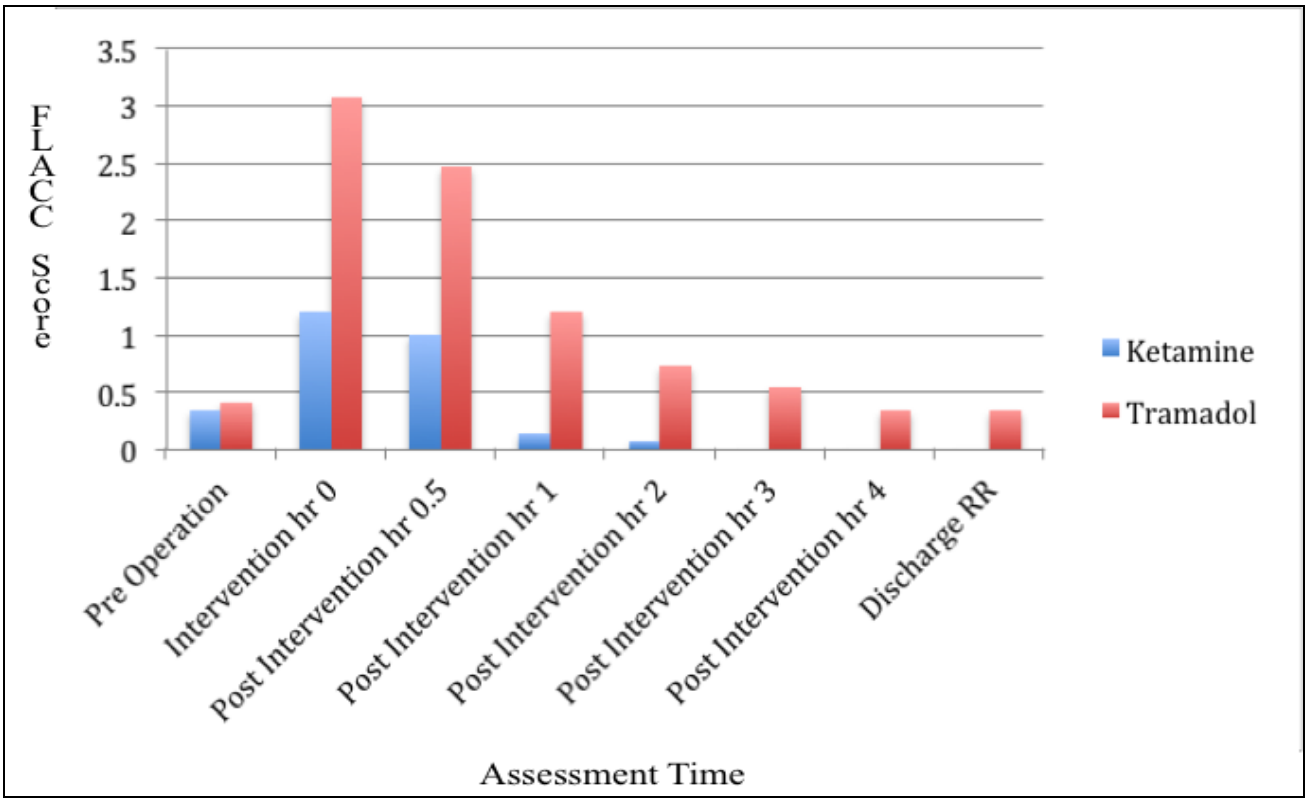

Figure 3. FLACC Score During the Intervention of Both Groups

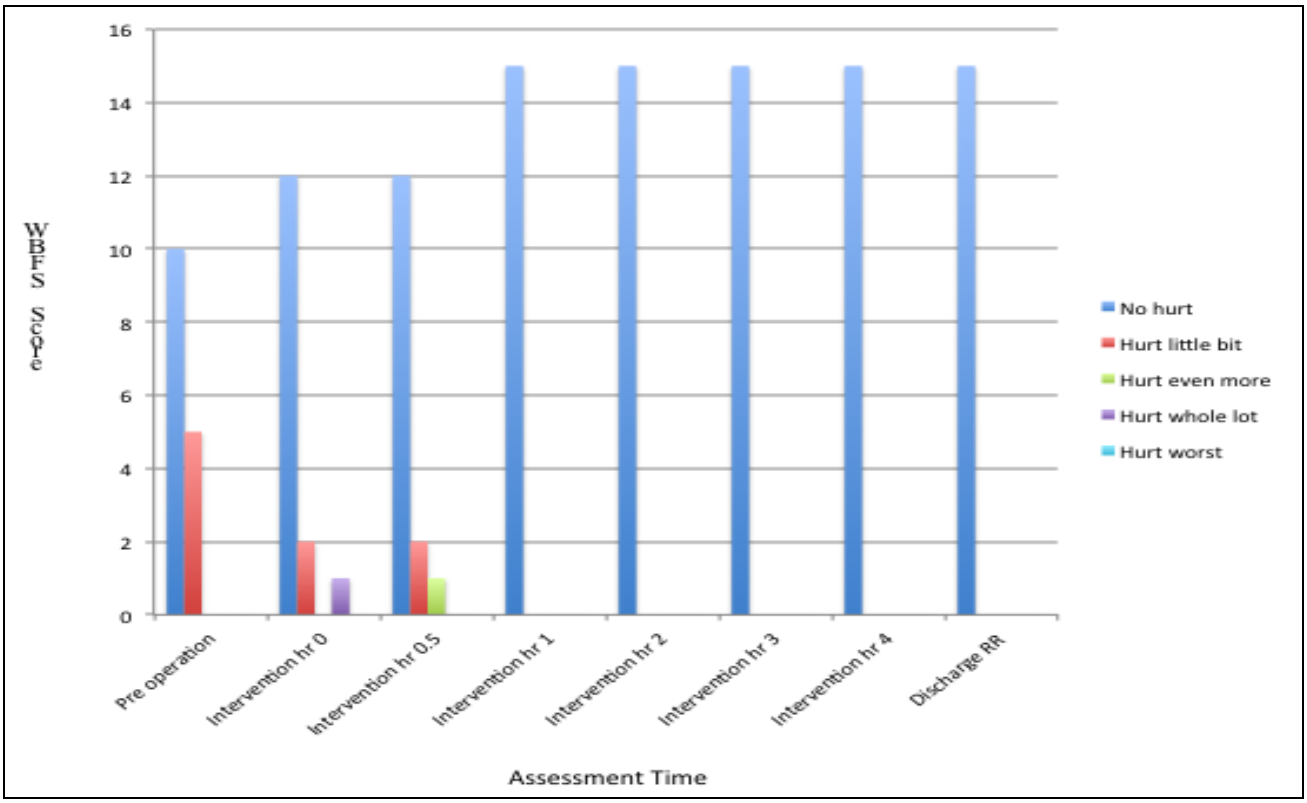

Figure 4. WBFS Score During the Intervention in the Ketamine Group

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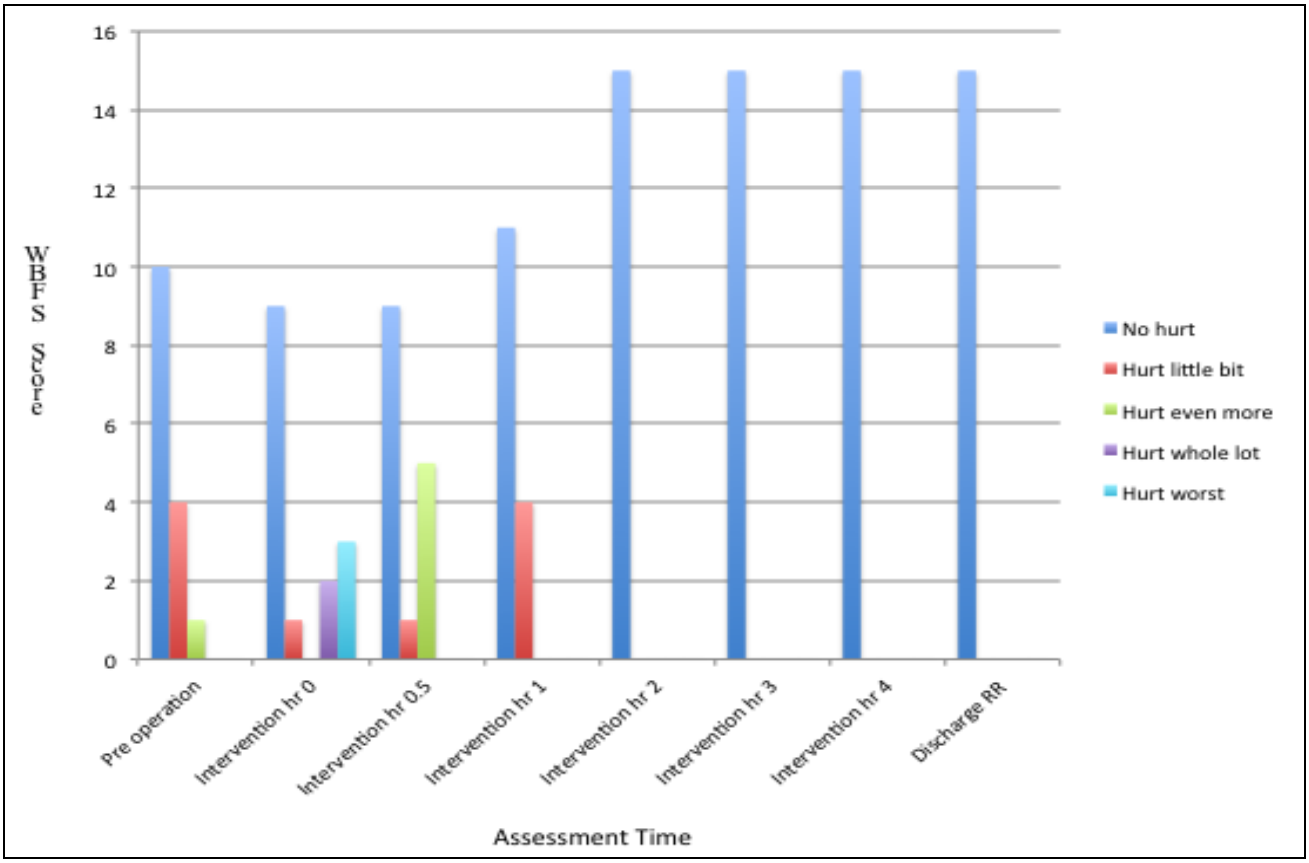

Figure 5. WBFS Score During the Intervention in Tramadol Group

Rescue analgesics in form intravenous fentanyl were given to one patient (6.7%) in the ketamine group and 4 patients (26.7%) in the tramadol group with $p > 0.05$. One patient (6.7%) in the ketamine group experienced vomiting as a drug side effect, whereas 2 patients (13.3%) in the tramadol group experienced nausea and 3 patients (20%) had vomiting with no significant differences.

Generally, oral analgesia was well accepted and comfortable for both parents and children. The measuring instruments used are WBFS Scale and FLACC Scale, as they are simple, have been widely recognized and used. Pain in children of kindergarten age (pre-schoolers) and school-age is most precisely rated with behavioral observation (11). The use of FLACC is felt to be the most appropriate method of pain assessment for children aged 5-10 years, while the use of WBFS depends on the subjectivity of the child, where the surrounding environment is very influential. Therefore, in this study the results of a pain assessment with WBFS were more homogeneous and cannot be assessed statistically or that there was no meaningful difference between the two groups.

The findings of this study showed that oral ketamine was better and more effective for postoperative pain in children compared to tramadol. Based on the FLACC parameter numerically (0-10 scale), there was no difference in FLACC pre-operation scale before surgery, 0-hour treatment, and 30 minutes after treatment. But there was a significant difference after 1 hour of intervention until the patient discharged from the recovery room ($p=0.04$). On 1 hour after intervention in the ketamine group had a lower FLACC scale compared to the tramadol group. As for the parameters of WBFS was not obtained meaningful differences between the

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two groups because the scale on WBFS was ordinal, so in this study which hadonly a small number of samples, the p-value was not significant. In addition to the pain assessment with the parameters of WBFS in 2 hours after intervention until the patient discharged from the recovery room could not be statistically analyzed because of a homogeneous sample (all research samples included in the scale were no pain).

In this study, the number of subjects that need rescue analgesics in the ketamine group was less than in the tramadol group. This can be caused by the difference in the pain level of the patient during surgery. Pain is complex, it depends on the family factors; how mothers educate the children in dealing with pain, culture absorbed in the child, newly known environment, and previous pain experience (3).

Based on this study, 1 patient in the ketamine group experienced a side effect of vomiting, while in the tramadol group obtained 2 patients who had nausea, and 3 patients experienced vomiting (Table 3). It is said in literature that both ketamine and tramadol can cause nausea and vomiting, as both drugs also work on opioid receptors (6). For ketamine, there are rare side effects of nausea and vomiting, since the primary target of the ketamine molecule is NMDA receptors. Ketamine inhibits these receptors thus lowering neuronal activity and can lead to anesthetic conditions (4). Also, the dose used for the analysis is not the amount of dose used for sedation and anesthesia, so the side effect is expected to be minimal. Oral tramadol can be absorbable quickly and has considerable bioavailability after the initial dose. Because after administration both intravenously and orally will achieve the highest concentration in a very fast time, so this causes nausea and vomiting to occur (6).

Table 3. Comparison of Side Effect Between Groups

Side Effects	Group A Ketamine n = 15 (100%)	Group B Tramadol n = 15 (100%)
No Side Effect	14 (93.3%)	10 (66.7%)
Nausea	0 (0%)	2 (13.3%)
Vomiting	1 (6.7%)	3 (20%)

CONCLUSION

Oral ketamine provided more effective for postoperative pain in children with minimum side effects compared to oral tramadol. The majority of patients in this group had less pain scores in the postoperative period in the recovery room. Further studies in bigger numbers may be needed to conclude whether oral analgesics are better to avoid trauma from injection in children.

Conflict of Interest

There is no conflict of interest in this study.

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Original Article

COMPARING ALTERATION OF MMSE (MINI-MENTAL STATE EXAMINATION) SCORES AS COGNITIVE FUNCTION TEST IN GERIATRICS AFTER GENERAL AND REGIONAL ANESTHESIA

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ABSTRACT

Introduction: An alteration of cognitive function in geriatrics often occurred after a surgery procedure. To do a surgery, patients would go through the process with anesthesia, whether it is general or regional anesthesia. We aimed to identify the effect of general and regional anesthesia in increasing the risk of alteration in cognitive function from geriatrics who underwent elective surgery followed by other risks. **Material and Method:** This observational analytic study has a total sample of 60 patients who aged 60 years or more, and half of the total sample underwent an elective surgery with general anesthesia, whereas the other half with regional anesthesia at Integrated Central Surgical Building of Dr. Soetomo General Academic Hospital in a range of October – November 2016. The cognitive function of patients was assessed with MMSE which is done in approximately 10 – 15 minutes. **Result and Discussion:** There was a statistically significant correlation between age and both preoperative MMSE score also the alteration of MMSE score after 3 days in patients with regional anesthesia (P-value = 0.032; 0.044). Also, the correlation between educational status and preoperative MMSE score (P-value = 0.001). There was also a statistically significant difference in alteration of the MMSE score after 3 days between patients with general and regional anesthesia which went through the hypotension phase (P-value = 0.022; 0.003). We identified that both general and regional anesthesia could lead to alteration of MMSE score (P-value = 0.001; 0.02) and there was a statistically significant difference between both of them (P-value = 0.001). **Conclusion:** Both general and regional anesthesia could lower the cognitive function of geriatrics, especially general anesthesia which happened to have a higher risk to occur. Other factors such as age, educational status, and hemodynamic condition during surgery, had their impacts toward lowering cognitive function in geriatrics.

Keywords: Postoperative Cognitive Function; General Anesthesia; Regional Anesthesia; MMSE Score

ABSTRAK

Pendahuluan: Perubahan fungsi kognitif pada pasien geriatri sering terjadi setelah menjalani prosedur operasi. Untuk melakukan prosedur operasi, pasien akan melalui proses anestesi, baik anestesi umum maupun anestesi regional. Peneliti ingin mengetahui efek dari anestesi umum dan regional dalam meningkatkan risiko perubahan fungsi kognitif dari pasien geriatric yang menjalani operasi elektif diikuti dengan factor lainnya. **Metode dan Bahan:** Penelitian ini berdesain observasional analitik dengan jumlah sampel sebesar 60 pasien yang berusia 60 tahun atau lebih, dan setengah dari sampel tersebut menjalani operasi elektif dengan anestesi umum, sedangkan setengah lainnya dengan anestesi regional di Gedung Bedah Pusat Terpadu RSUD Dr. Soetomo dalam rentang waktu Oktober – November 2016. Fungsi kognitif pasien dinilai menggunakan MMSE Skor yang dilakukan sekitar 15-10 menit. **Hasil dan Pembahasan:** Terdapat hubungan yang bermakna antara usia pasien dengan skor preoperatif MMSE dan perubahan skor MMSE setelah 3 hari pada pasien dengan anestesis regional (nilai P = 0.032; 0.044). Juga terdapat hubungan yang bermakna antara status pendidikan pasien dengan skor awal MMSE (nilai P = 0.001). Ditemukan perbedaan yang bermakna antara skor MMSE setelah 3 hari pada pasien dengan anestesi umum dan regional yang mengalami fase hipotensi selama operasi berjalan (nilai P = 0.022; 0.003). Peneliti menemukan bahwa anestesi umum dan regional mampu menyebabkan perubahan terhadap skor MMSE (nilai P = 0.001; 0.02) dan terdapat perbedaan yang bermakna di antara keduanya (nilai P = 0.001). **Kesimpulan:** Kedua jenis anestesi, anestesi umum dan anestesi regional, mampu menurunkan fungsi kognitif pada pasien geriatri, terutama anestesi umum yang memiliki risiko lebih tinggi untuk terjadi. Faktor lain seperti usia pasien, status pendidikan pasien, dan kondisi hemodinamika selama operasi berlangsung, memiliki dampak masing-masing terhadap penurunan fungsi kognitif pada pasien geriatri.

Kata kunci: Fungsi Kognitif Pasca Operasi; Anestesi Umum; Anestesi Regional; Skor MMSE

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INTRODUCTION

In 2015, Indonesia reached 72 years for its life expectancy, increasing from 68.6 years in 2004. This achievement followed by an increase in geriatrics, which is 8.03% of Indonesia's total population. (1)

Attention is needed to be given more in health care towards geriatrics, such as surgery. To do surgery, we need to pay more attention to giving its anesthesia because the morbidity and mortality risks in geriatrics are higher than young adults or adults. The comprehensive and multidiscipline of evaluation in preoperative and postoperative will produce a greater outcome in geriatrics.

Postoperative complications may come in vary; central nervous system dysfunction, postoperative delirium, and postoperative cognitive dysfunction (POCD) are the most common complications in geriatrics. Delirium and POCD are usually acute and reversible if it's taken care of seriously. However, inadequate diagnosis and treatment will lead its condition to dementia.

Dementia is a neurodegenerative disorder caused by the damage of the neurons in important areas of the brain, including the hippocampus, parietal lobe, and temporal lobe. Some studies concluded that postoperative dementia happened because of an inflammatory process as a reaction towards the surgery or anesthesia itself. It's been proved by increasing pro-inflammatory mediators and cytokines in cerebrospinal fluid. Likewise, another study showed an inflammation happened in the hippocampus of a postoperative patient, which is associated with memory. (2)(3)

Potential neurotoxicity of general anesthesia to cause dementia is still a controversy. Inhalation anesthesia is suspected to increase Aβ protein plaque formation and neuro fibrillation which are included in the pathogenesis of dementia. (4)(5) Several studies used mice to prove that Isoflurane inhalation increased the risk of getting POCD and dementia after surgery. (6)(7)

Researchers hypothesized that regional anesthesia should be an alternative to reduce the incidence of POCD in geriatrics. A study conducted by Mandal et al. (8) showed that an assessment of cognitive function in hip and knee surgery among geriatrics using MMSE has better results in patients with regional anesthesia rather than general anesthesia. Rasmussen et al. (9) agreed with their study also concluded that the incidence of POCD was bigger in patients with regional anesthesia after 7 days of surgery. However, Russo et al. (10) had a different result with no significant difference in cognitive function between regional and general anesthesia of postoperative patients who underwent total knee replacement surgery. Nineteen randomized trials have been reviewed by Wu et al. (11) and only one study which showed a significant difference in cognitive function between regional and general anesthesia of postoperative patients.

Mini-Mental State Examination (MMSE) is a cognitive function test that is widely used because of its simplicity in evaluating clinical conditions of patients with dementia and cognitive dysfunction. (12) Using this test, we aimed to identify the effect of general and regional anesthesia in increasing the risk of alteration in the MMSE score from geriatrics who underwent elective surgery.

MATERIAL AND METHOD

This observational analytic study has a total sample of 60 patients who aged 60 years or more, underwent an elective surgery apart from open-heart surgery or neurosurgery, and

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being done at Gedung Bedah Pusat Terpadu Dr. Soetomo General Hospital in a range of October – November 2016. Half of the total sample underwent surgery with general anesthesia, whereas the other half with regional anesthesia.

There have been exclusion criteria of the sample in this study, such as: had a central nervous system dysfunction, had a mental disorder, had an addiction towards hypnotic-sedative medication, opioid, or alcohol, also a complication happened during or after surgery.

General and regional anesthesia were the independent variables of this study. Followed by the dependent variables which were MMSE score before surgery, 3 days after surgery, and 7 days after surgery. However, several patients tended to go home 5 – 6 days after surgery. The cognitive function of patients was assessed with MMSE which is done in approximately 10 – 15 minutes.

The data of this study were analyzed with SPSS Statistics 17.0. Paired t-test, Wilcoxon test, and Mann-Whitney test were used in this study.

RESULT AND DISCUSSION

The total sample was 60 elderly patients and above 60 years old. Out of 30 patients who underwent elective surgery with general anesthesia, 11 were male patients. Whilst out of 30 other patients with regional anesthesia, male patients were dominating with 17 in total. Based on the result of the Chi-Square test, there was no statistically significant difference between gender and all MMSE scores (P-value = 0.911; 0.871; 0.654), this result showed that males and females have similar probability to encounter dementia.

In patients with general anesthesia, 26 patients had an age range of 60 – 69 years old, whereas 2 patients each in the age range of 70 – 79 years old and 80 years old. Twenty patients also dominated in the age range of 60 – 69 years old, followed by 9 patients in the age range of 70 – 79 years old, and 1 patient aged 80 years.

Table 1. The Correlation between Age Range and Preoperative MMSE Score

Age Range	Preoperative MMSE Score (n=60)			P-Value
	11 – 20	21 – 26	27 – 30	
60 – 69	1 (1.67%)	30 (50%)	15 (25%)	0.032*
70 – 79	0 (0%)	9 (15%)	2 (3.33%)	
≥80	1 (1.67%)	2 (3.33%)	0 (0%)	

*Chi-Square test

Table 2. The Correlation between Age Range and Alteration of MMSE Score After 3 days in patients with General and Regional Anesthesia

Age Range	General Anesthesia (n=30)			P-Value	Regional Anesthesia (n=30)		P-Value
	0	1-2	3-4		0	1–2	
60 – 69	4 (13.3%)	17 (56.6%)	5 (16.7%)	0.138*	18 (60%)	2 (6.7%)	0.044*
70 – 79	0 (0%)	0 (0%)	2 (6.7%)		6 (20%)	3 (10%)	
≥80	0 (0%)	1 (3.3%)	1 (3.3%)		0 (0%)	1 (3.3%)	

*Chi-Square test

Based on table 1, there was a statistically significant correlation between age and preoperative MMSE score after being tested with the Chi-square test (P-Value = 0.032). Table 2 showed that there was no correlation between age and the alteration of the MMSE score after 3 days in patients with general anesthesia (P-value = 0.138). But, we got a different value for the regional anesthesia group. There was a significant correlation between age and the alteration of the MMSE score after 3 days in patients with regional anesthesia (P-Value = 0.044). This result was similar to a study conducted by Crosby et al.

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(13) which showed a decline of brain mass from 95% in young adults to 80% in geriatrics. Neurons happened to shrink in size, a number of synapses, and dendritic complexity. Aging was hypothesized to decrease the functional brain which led into dementia. (13)(14)

Eleven patients in general anesthesia group were dominating with educational status as Junior High School alumni, whereas the same number of patients were equally dominating with educational status as Junior High School alumni and Elementary School alumni with a total of 12 patients each in regional anesthesia group.

Table 3. The Correlation between Educational Status and Preoperative MMSE Score

Educational Status	Preoperative MMSE Score (n=60)			P-Value
	11 – 20	21 – 26	27 – 30	
Undergraduate	0 (0%)	0 (0%)	3 (5%)	0.001*
Senior High School	0 (0%)	1 (1.67%)	8 (13.3%)	
Junior High School	0 (0%)	18 (30%)	5 (8.33%)	
Elementary School	1 (1.67%)	19 (31.7%)	1 (1.67%)	
Didn't Graduate Elementary School	1 (1.67%)	2 (3.33%)	0 (0%)	

*Chi-Square test

Based on Table 3 there was a statistically significant correlation between educational status and preoperative MMSE score after being tested with the Chi-Square test (P-value = 0.001). Emily Sharp et al. conducted a study which showed that a higher educational status reflected a higher capacity and better cognition of the brain, it would decrease the risk of dementia to happen. Cognitive reserve theory hypothesized that a person with low educational status was more susceptible to experience brain damages compared to the ones who had a higher educational status. (15) The different result was getting from the correlation between Educational status and the alteration of MMSE Score both in general dan regional anesthesia. There was no statistically significant correlation with P-Value = 0.223 (general anesthesia) and P-Value = 0.572 (regional anesthesia).

Most of the patients both in general and regional anesthesia group suffered from hypotension phase during surgery, with 22 patients in general anesthesia group and 25 patients in the other.

Table 4. The Correlation between Hypotension and Alteration of MMSE Score After 3 Days in Patients with General Anesthesia

Hypotension	MMSE Score after 3 days (General anesthesia) (N=30)			P-Value
	0	1 – 2	3 – 4	
Yes	0 (0%)	3 (10%)	5 (16.7%)	0.022*
No	4 (13.3%)	15 (50%)	3 (10%)	

*Chi-Square test

Table 5. The Correlation between Hypotension and alteration of MMSE score after 3 days in patients with regional anesthesia

Hypotension	MMSE Score after 3 days (Regional anesthesia) (N=30)		P-Value
	0	1 – 2	
Yes	1 (3.33%)	4 (13.3%)	0.003*
No	23 (76.7%)	2 (6.67%)	

*Chi-Square test

Based on Tables 4 and 5, there was a statistically significant correlation in the alteration of the MMSE score after 3 days between patients with general and regional anesthesia which went through the hypotension phase after being tested with Chi-Square test (P-value = 0.022; 0.003). This result was similar to a study conducted by Doods et al. (16), which after 5 days of retropubic prostatectomy surgery, the patients

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who went through the hypotension phase during surgery had a lowering cognitive function then recovered in the sixth week.

The duration of anesthesia given to each group of patients was mostly done below or equal to 180 minutes. Only 8 patients were given general anesthesia above 180 minutes, whereas regional anesthesia was given to only 6 patients. There was no statistically significant correlation between the duration and alteration of the MMSE score in both groups after being tested with the Chi-Square test (P-value = 0.378). Gelmanas et al. (17) had a similar result concerning the same variable.

Table 6. The Comparison between the preoperative and after 3 days MMSE Score in General and Regional Anesthesia

MMSE Score	General Anesthesia (n=30)		Regional Anesthesia (n=30)	
	Mean±SD	P-Value	Mean±SD	P-Value
Preoperative	25.13±2.801	0.001*	24.8±2.52	0.02**
After 3 days	23.43±3.431		24.6±2.68	

*paired T-Test **Wilcoxon Test

Table 7. The Comparison between the MMSE Score of General and Regional Anesthesia

The Kind of Anesthesia	MMSE Score	
	Mean±SD	P-Value
General Anesthesia	1.7 ± 1.088	0.001*
Regional Anesthesia	0.23 ± 0.504	

*Mann-Whitney test

Based on the result of Paired T-Test, there was significant difference between preoperative and after 3 days MMSE Score in General anesthesia patient (P-Value = 0.001). The Regional anesthesia group tested with the Wilcoxon test and there was significant difference between preoperative and after 3 days MMSE Score (P-Value = 0.02) (Table 6). We also identified that there was a statistically significant difference between the alteration of the MMSE score with general and regional anesthesia after being tested with the Mann-Whitney test (P-value = 0.001). In other words, a lowering cognitive function would happen more often in patients with general anesthesia compared to the patients with regional anesthesia.

With several remaining data of patients who were still available until 7 days after the surgery, 33% of patients in the general anesthesia group happened to lose 2 points of their MMSE score and the rest only lost 1 or 0 points. Even in regional anesthesia group, no patient was found with an alteration of the MMSE score. This result might lead to the hypothesis of reversible lowering cognitive function.

CONCLUSION

Both general and regional anesthesia could lower the cognitive function of geriatrics, especially general anesthesia which happened to have a higher risk to occur. Other factors such as age, educational status, and hemodynamic condition during surgery, had their impacts toward lowering cognitive function in geriatrics.

Conflict of Interest

There is no conflict of interest in this research nor on the writing of the article.

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Case Report

MYASTHENIA CRISIS VS CHOLINERGIC CRISIS: CHALLENGES IN CRISIS MANAGEMENT WITHOUT PLASMAPHERESIS OR INTRAVENOUS IMMUNOGLOBULIN (IVIG)

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ABSTRACT

Introduction: Myasthenia gravis (MG) is an acquired autoimmune disease that clinically characterized by weakness & fatigability exertion in skeletal muscle with prevalence as high as 2–7 in 10,000 and women are affected more frequently than men (~3:2). Over 12-16% of generalized MG patients experience crisis once in their lifetime. Respiratory failure is a serious complication of myasthenia gravis that may be caused by an exacerbation of myasthenia (myasthenia crisis) or an excess treatment of a cholinesterase inhibitor (cholinergic crisis). **Case Report:** Thirty-two years old woman refereed from a private hospital to ED for further treatment with myasthenia in crisis, after nine days of treatment in the previous ICU. Patient already in intubation with mechanical ventilation and history of the treatment of high dose of multiple anticholinesterase drug and steroid without plasmapheresis or immunoglobulin intravenous. During admission, diarrhea was present, with no sign of GI infection. On the third day of admission, the patient performed Spontaneous Breathing Trial and was a success then extubated. Then two day after extubation, the patient falls to respiratory failure and need mechanical ventilation. Anticholinesterase test was performed, and it shows no improvement in clinical signs, and diagnose as Cholinergic Crisis. After re-adjustment of anticholinesterase drug with a lower dose, clinically, the respiratory condition improved, and on the 10th day of admission, the patient was succeed extubated. At 12nd days of ICU admission, patient discharge from ICU. **Discussion:** Myasthenia and Cholinergic Crisis is a life-threatening condition that characterized by generalized respiratory muscle weakness that requires ventilatory support. Respiratory failure may be present in cholinergic crisis without cholinergic symptoms, such as miosis, diarrhea, urinary incontinence, bradycardia, emesis, lacrimation, or salivation. The most important management aspect of Myasthenia patients in crisis is the recognition and treatment of myasthenia vs cholinergic crisis.

Keyword: Myasthenia Crisis; Cholinergic Crisis; Plasmapheresis; Intravenous Immunoglobulin; Anticholinesterase Inhibitors

ABSTRAK

Pendahulun: Myasthenia gravis (MG) adalah gangguan kelemahan otot lurik karena aktifitas yang disebabkan kelainan autoimun dengan prevalensi 2-7 kasus tiap 10.000 orang dan lebih sering terjadi pada wanita (3:2). Sekitar 12-16% pasien MG akan mengalami minimal 1 kali periode krisis, yang merupakan komplikasi berbahaya yang menyebabkan gagal napas. Kondisi ini dapat terjadi karena adanya memburuknya MG (krisis Miastenia) atau *overdose* obat *cholinesterase inhibitor* (Krisis Cholinergik). **Case Report:** Wanita 32 tahun rujukan dari ICU RS Swasta dengan krisis miastenia untuk perawatan lanjutan setelah perawatan 9 hari. Pasien dengan Ventilator dan riwayat penggunaan berbagai jenis obat *anticholinesterase inhibitor* dosis tinggi dan steroid. Saat di UGD, pasien mengalami diare tanpa ada tanda-tanda infeksi saluran cerna. Pada hari ketiga perawatan ICU, pasien dapat lepas dari Ventilator setelah berhasi dilakukan *spontaneous breathing trial*. Namun dua hari setelah ekstubasi, pasien kembali mengalami gagal napas dan dilakukan intubasi ulang. Tes anticholinergic dilakukan dengan hasil mengarah pada krisis cholinergic. Setelah pengaturan ulang dosis obat anticholinesterase, kondisi klinis membaik dan pada hari ke-10 pasien lepas dari ventilator. Pasien pindah dari ICU setelah 12 hari perawatan. **Diskusi:** Krisis Miastenia – Cholinergik (KMC) adalah kondisi *life threatening* yang ditandai oleh kelemahan otot pernapasan yang menjadi gagal napas. Gagal napas pada krisis cholinergic dapat terjadi meskipun tidak diikuti oleh tanda atau gejala cholinergic yang lain (miosis, Diare, Inkontinesia urin, bradikardi, emesis, atau salivasi). Penatalaksanaan paling penting pada pasien miastenia pada kondisi krisis adalah identifikasi dan penanganan awal pada KMC.

Kata Kunci: Krisis Myastenia; Krisis Kolinergik; *Plasmapheresis*; *Intravenous Immunoglobulin*; *Anticholinesterase Inhibitor*

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INTRODUCTION

Myasthenia crisis is a myasthenia gravis' (MG) complication that characterized by worsening of skeletal muscle weakness which is resulting in respiratory failure that requires intubation and mechanical ventilation. (1) The cholinergic crisis is an emergency that is mainly characterized by flaccid paralysis and respiratory failure, which mainly occurs due to improper administration or intake of anticholinergic agents in MG patients. (2) The worldwide incidents are about 8 to 20 cases per 100,000 people. (3) Crisis periods occur on 15-20% of myasthenia patients, at least once in their lives. First crisis occurs on 8-12 months from onset of MG with 5% mortality rate. (1)(4)

In the last three to four decades the use of cholinesterase inhibitors drug has been less in moderate to severe and/or crisis, certainly not as a single treatment. Because cholinesterase inhibitors may have a different half-life in critically ill patients which resulting in absorption decreasing of enteral formulations. Increased weakness and interference with extubation may be lead by overdose of these drugs with the resulting incident of cholinergic crisis with or without other cholinergic symptoms. (5)(6) Plasmapheresis or Intravenous Immunoglobulin (IVIg) is the gold standard of MG therapy in crisis, and most guidelines not recommended continuity of cholinesterase inhibitors during the crisis. (3)-(5)(6)

CASE REPORT

Thirty-two years old woman refereed from a private hospital to ED for further treatment with myasthenia in crisis and suspect pneumonia, after nine days of treatment in the previous ICU. Patient already in intubation with mechanical ventilation (MV) and history of the treatment of high dose of multiple anticholinesterase drug, Pyridostigmine oral 60mg every 4 hours, Neostigmine iv. 0,5mg every 8 hours and steroid, methylprednisolone iv 62,5mg every 8 hours, without plasmapheresis, IVIg, or another immunosuppressant. The patient diagnoses with MG for 3 years with routine daily pyridostigmine oral without dose adjustment by a physician. A week before admission on the previous ICU, the patient got common cold for three days and a general weakness that resulting in dyspnea needed for MV.

During admission at Emergency Department, Dr. Soetomo General Academic Hospital, patient with Glasgow coma scale (GCS) E4 Mx V6 (with endotracheal tube), stable vital sign, assisted respiration with slight rhonchi in a small area in both lung and from muscle strength grading examination, superior and inferior extremity got scale 5 out of 5 and 2-4 out of 5 with mean motoric strength grade were 4 out of 5. Other signs and symptoms are diarrhea without signs of intestinal infection. Form laboratory (Table 1) and radiology examination (figure 1), there are increased white blood count and liver function test with other normal blood laboratory and normal chest x-ray.

Diarrhea still present for the first two days of treatment in ICU and muscle weakness getting worse with mean extremity motoric strength grade was below 3 out of 5. Pyridostigmine dose were reduced to 60 mg every 8 hours. The next day evaluation, diarrhea has already stopped but there is no improvement on muscle strength scale, so based on clinical judgment, the dose of

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pyridostigmine was increased into double dose (60 mg every 4 hours). After increasing dose, muscle strength grade was increased and the spontaneous breathing trial was performed successfully.

Tabel 1. Routine Laboratory Result at Emergency Department

Laboratory examination	Value
Hemoglobin	15,9 g/dL
Haematocrit	47 %
White Blood Count	19.900 x 10^9/L
Blood Sugar	132 mg/dL
SGOT	45 U/L
SGPT	208 U/L
Urea	15mg/dL
Creatine	0,54 U/L
Natrium	140 mmol/L
Kalium	4,66 mmol/L
Chloride	93 mmol/L

Pyridostigmine dose was re-adjusted by reducing a half and the patient was extubated on the third day of ICU treatment. After 24 hours extubating, patient show tachypnea until 30-35 breath per-minute with a stable vital sign and without muscle weakness and any cholinergic sigh (such as hypersalivation, diarrhea, miosis, and hyper-lacrimation).

The anticholinergic test was performed by using neostigmine 0,5 mg iv. and the result was positive by decreased respiration rate until normal, then pyridostigmine dose was increased by 60 mg every 4 hours. Even though the PaO2/FiO2 ratio was 230 before the Anticholinergic test, the clinically respiration condition was getting better after the test, so the patient are not re-intubation for observation. But the next day, another tachypnea episode happened again with the patient unable to cough and fall to respiratory failure. This episode was followed by muscle weakness. The patient was re-intubate and pyridostigmine dose was increased twice as

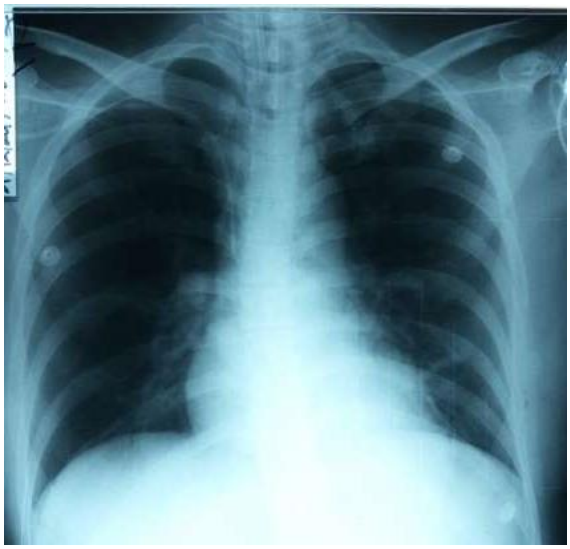

Figure 1. Chest X-ray at the Emergency Department. There is no sign of Pneumonia, normal Chest X-ray

before (120 mg every 4 hours). Chest X-ray after re-intubation shows sputum retention with a decrease of PaO2/FiO2 Ratio (288).

Re-adjustment dose was based on an anticholinergic test that performed the previous day, and no sign of cholinergic activity at all. After two days of re-intubate, muscle weakness was getting worse and still, there was no signs of cholinergic activity. Re-adjust pyridostigmine dose was doing by reducing it with the assumption it could be caused by the cholinergic crisis. We gradually decrease the dose, on the first day reduce to 60 mg every 4 hours, then every 8 hours. On the eighth to ninth days of ICU treatment or third to fourth days after re-intubate, muscle strength was increase and patient able to be wean from mechanical ventilation.

On the tenth days of ICU treatment, patients were extubated and pyridostigmine dose were adjusted slightly increased (60 mg every 6 hours) to prevent possible another myasthenia crisis (dose too low) with the precaution of cholinergic dose (dose too high).

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Evaluation after re-adjustment of anticholinesterase drug with a lower dose, clinically, respiratory condition, and muscle strength were improving (detail Figure 2).

Corticosteroids (CSs) therapy were given continually with methylprednisolone iv. 125 mg every 6 hours, and tapering down at ward. After the twelfth days of ICU treatment, patient discharge from ICU and move to neurology ward, and chest x-ray on the fifteenth days of hospital admission shows normal result.

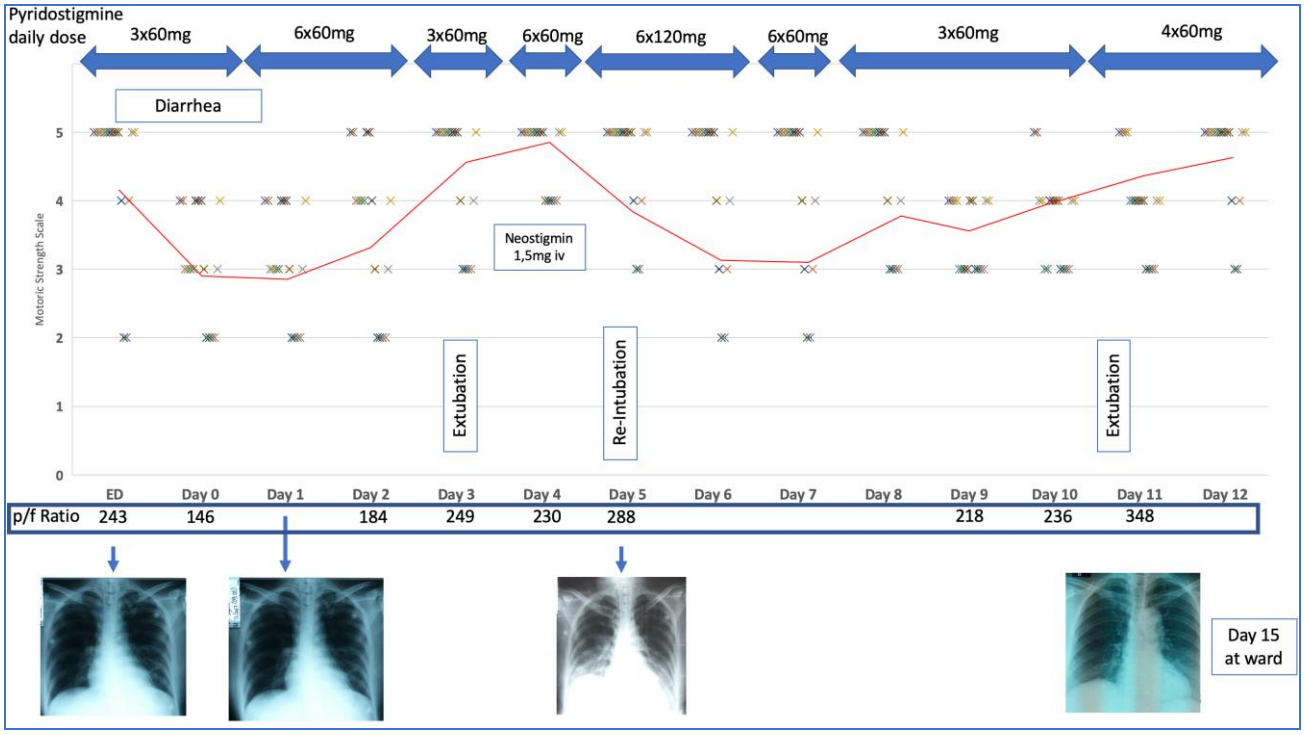

Figure 2. Progress of muscle strength, Pyridostigmine daily dose, PaO2/FiO2 ratio, Chest X-Ray during Hospital Admission

DISCUSSION

The pathogenesis of MG is the absent of acetylcholine receptors (AChRs) on the postsynaptic membrane of the neuromuscular junction (NMJ) because of the production of AChR and/or muscle-specific receptor tyrosine kinase (MuSK) antibodies (Abs), which as the result of the loss of postsynaptic AChRs and associated with NMH destruction. (8) Since the uses of corticosteroid (CSs) as MG treatment in the 1950s, Immunomodulating therapies, such as plasmapheresis, IVIg, and immunosuppressant, have replaced Acetylcholinesterase inhibitors (AChEIs) as sole therapies in crisis. (3)(5)(8)(9) AChEIs work as enzyme Acetylcholinesterase (AchE) competitive blockade in the extracellular matrix of the folded postsynaptic muscle endplate membrane. The result of these actions are the breaks down of Acetylcholine (ACh) into choline and acetate, the inactive metabolites of ACh. Pyridostigmine, that available in 60-mg tablets, is one of the most commonly used drug, which begins to work 30 minutes after oral administration and duration of action about 3-6 hours. (8)

AChEIs induce the corresponding adverse cholinergic effects on both muscarinic and nicotinic synapses, such as gastrointestinal

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tract hypermotility (e.g., abdominal pain, diarrhea, etc.), hyper-salivation and respiratory hyper-secretions, hyperhidrosis, and bradycardia or arrhythmia. Overtreatment of AChEIs may give rise to a serious cholinergic crisis (e.g., respiratory failure), which results from overactivity of neuromuscular transmission by excessive ACh.

The cholinergic crisis is uncommon because most of the guidelines suggest to stop AChEIs when crisis period occurs, but the cholinergic crisis is still an important evaluation of the patient in myasthenic crisis in received AChEIs treatment. (1)(8)(9) Randomized controlled trials in myasthenic crisis have been limited, perhaps because MG is a rare disease and difficult to recruit many suitable patients. Because of these reasons, most physicians have chosen immunotherapies that available within their medical environments and based on their own clinical experiences. (8)

Patients cannot be therapeutic with plasmapheresis or IVIg because they are not financially able and do not have insurance. So, even though at the crisis, the only option was AChEIs and corticosteroids (CSs). CSs are commonly used as the first-line drug as Immunosuppressants (IS). The reason using these drugs is for inducing comparatively rapid remission and bridging to long-term maintenance therapy using other ISs or immunomodulators until the onsite of these drugs. CSs are used in conjunction with AChEIs. High-dose methyl prednisolone may be initiated at the same time with AChEIs since the effect of methylprednisolone happens after 2 weeks. (1) The use of High-dose corticosteroids in MG patients should be performed with caution, as this drug can worsening of weakness in non-ventilated patients, around one-third of the cases. In the mechanical ventilated patient, the initiation or the escalation of these drugs should be considered. (10)

Tabel 2. Myasthenia Crisis versus Cholinergic Crisis

	Crisis	
	Myasthenia	**Cholinergic**
Focal or generalized muscle weakness	+	+
Respiratory difficulty or failure	+	+
Cholinergic symptoms and signs		
Diarrhea	-	+/-
Urinary Incontinentia	-	+/-
Miosis	-	+/-
Bronchospasm/Bronchorrhea	+/-	+/+
Bradycardia	-	+/-
Emesis	-	+/-
Salivation	-	+/-
Lacrimation	-	+/-
AChEIs Test	+	-

Source: Hetherington KA (6)

The most difficult part was recognizing and differentiating between Myasthenia Crisis (MC) versus Cholinergic Crisis (CC) (detail table 2). Both myasthenia and cholinergic crisis can be present as respiratory failure. Triggers for MC include disease exacerbations, noncompliance with AChEIs medication, adverse effects of other medications, fever, and emotional stress. CC is secondary to excess AChEIs. In these cases, Ach could over-stimulation of striated muscles at the NMJ, which results in flaccid muscle paralysis that can be clinically indistinguishable from weakness caused by MC.

Respiratory failure may be present in the cholinergic crisis without other cholinergic symptoms, such as miosis, diarrhea, urinary incontinence, bradycardia, emesis,

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lacrimation, or salivation. Therefore, as with all seriously ill patients, priority is given to establishing and maintaining an airway and assuring adequate breathing. The respiratory status of a patient with myasthenia or cholinergic crisis can worsen unpredictably. Close monitoring of the patient's respiratory status and dose adjusting of AChEIs are mandatory. (1)(4)(6)(11)

CONCLUSION

Both myasthenia and cholinergic crisis can be present as respiratory failure. Respiratory failure may be present in the cholinergic crisis without other cholinergic symptoms and signs. Close monitoring of the patient's respiratory status and dose adjusting of AChEIs are mandatory and challenging.

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Case Report

INTRACRANIAL HEMORRHAGE IN PATIENTS WITH HEMOPHILIA A

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ABSTRACT

Introduction: Intracranial hemorrhage in inherited bleeding disorders is a medical emergency. The location of bleeding in most children is subdural and the most common cause is hemophilia. Although intracranial bleeding that occurs in people with hemophilia ranges from less than 5% of events, it is a life-threatening medical emergency so appropriate treatment is needed. **Case Report:** A boy patient 11 years old, 20kg weights have a seizure at home and followed by a decrease in consciousness. It was founded abnormalities in the form of anemia, prolonged FH (PPT 4x and APTT 4x), and hypocalcemia. The patient then was given main therapy; FVIII 100 IU/dL according to the FVIII target level calculated. The therapy continued with 500IU/12 hours according to the daily target of FVIII 50IU/dL. **Discussion:** The patient's condition was getting better day by day. The patient's consciousness started to improve after 14 days of postoperative. One month after that, the patient received *koate* treatment as the episodic handler. Diagnosing the exact cause in patients who have intracranial hemorrhage provides appropriate management so that the patients could be helped. **Conclusion:** Good collaboration between anesthesiologists, neurosurgeons, and pediatrics will increase the probability of successful management of critical bleeding without major sequelae.

Keywords: Intracranial Hemorrhage; Hemophilia; FVIII Therapy; Bleeding Therapy

ABSTRAK

Pendahuluan: Perdarahan intracranial akibat kondisi penyakit bawaan (turunan) merupakan sebuah kondisi kegawatdaruratan. Lokasi perdarahan yang paling sering terjadi pada anak – anak adalah perdarahan subdural dan penyebab terseringnya adalah hemophilia. Meski perdarahan intracranial yang terjadi akibat hemofilia kurang dari 5% kejadian, namun hal tersebut merupakan kondisi mengancam nyawa yang membutuhkan penanganan yang tepat. **Laporan Kasus:** Seorang anak laki – laki usia 11 tahun, berat 20kg, mengalami kejang dan penurunan kesadaran secara mendadak di rumahnya. Pasien dibawa ke rumah sakit dan mendapatkan penanganan. Dari pemeriksaan laboratorium, didapatkan anemia, pemanjangan FH (PPT 4x dan APTT 4x), dan hipokalsemia. Pasien diberikan FVIII 100 IU/dL berdasarkan penghitungan target FVIII. Terapi dilanjutkan dengan terapi lanjutan (maintainance) 500IU/12 jam sesuai dengan target harian FVIII 50 IU/dL. **Pembahasan:** Kondisi pasien berangsur – angsur membaik. Kesadaran pasien meningkat sejak 14 hari setelah operasi. Satu bulan kemudian, pasien menerima *koate* sebagai terapi lanjutan untuk pencegahan serangan perdarahan berulang. Diagnosis yang tepat dapat membuat pasien yang mengalami perdarahan intracranial mendapatkan penangnan yang tepat, sehingga pasien dapat tertolong. **Kesimpulan:** Kolaborasi yang baik antara dokter spesialis anestesiologi, dokter spesialis bedah saraf, dan dokter spesialis anak dapat meningkatkan kemungkinan keberhasilan dari suatu manajemen kondisi perdarahan kritis tanpa meninggalkan sekuele.

Kata Kunci : Perdarahan Intrakranial; Hemofilia; Terapi Faktor VIII; Terapi Perdarahan

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INTRODUCTION

Intracranial bleeding in inherited bleeding disorders is a medical emergency. (1) The location of bleeding in most children is subdural and the most common cause is hemophilia. (2) Although Intracranial Bleeding that occurs in people with hemophilia tends to be less than 5% of events, it is a medical emergency that requires the necessary soul needed. (1)(2)

Hemophilia is a disorder of X-linked congenital bleeding caused by a lack of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B). This lack of coagulation factor is due to mutations from the clotting factor gene.(1) the incidence is around

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1 in 10,000 births. Based on the World Federation of Haemophilia's (WFH) annual global survey shows that the hemophilia sufferers around the world were 400,000 in 2012. Hemophilia A dominates hemophilia B, about 80-85% of the total patients were suffered Hemophilia A. Hemophilia commonly happens in boys than girls. However, the F8 and F9 genes are susceptible to mutation which explains why a third of cases have no prior family history. (1)(3)

The right diagnosis provides the right management. Hemophilia presumed in patients who have an easy bruising history in their early childhood, spontaneous hemorrhage, especially internal hemorrhage such as hemorrhage in joints (70-80%), muscle (10-20%) and soft tissue (5-10%) where symptoms of bleeding occur when the child starts learning to walk or run. (1) In patients with mild hemophilia, excessive bleeding usually occurs after trauma or surgery. Family history of hemorrhage in about twothirds of total patients. A definitive diagnosis depends on the factor test to show FVIII or FIX deficiency. (1)(3)

CASE REPORT

A patient of a boy, 11 years old, weighing 20 kg, had a seizure at home and was followed by a decrease in consciousness at home and taken to the nearest hospital and treated. During treatment at the hospital, abnormalities such as anemia, longitudinal FH (4x PPT and 4x APTT) were found, and hypocalcemia was then given a PRC transfusion, vitamin K injection, calcium gluconate injection. The results of other examinations found that SDH appeared without the occurrence of trauma with 1.3 cm thick and MLS 1 cm which had been indicated as being operated (Thickness of cm1 cm and MLS $\geqslant$ 0.5 cm) but not due to blood coagulation abnormalities.

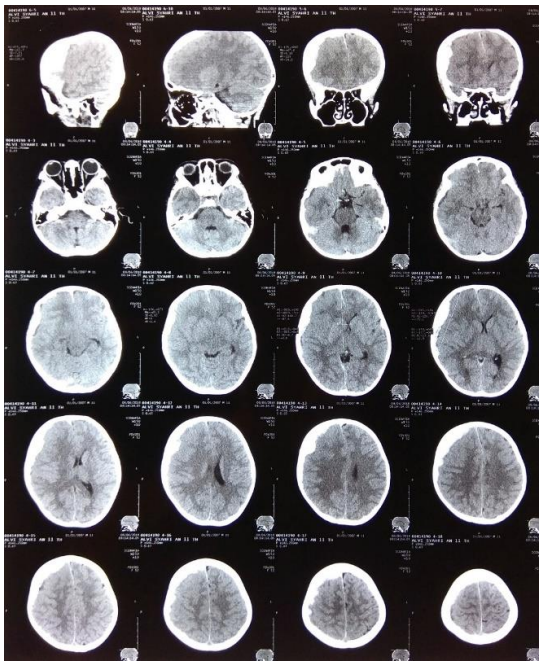

Figure 1. The CT Scan of Patient's Head Transverse View

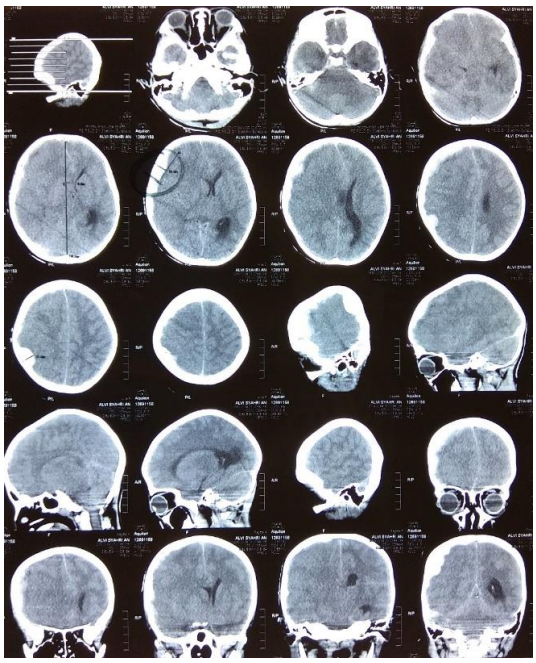

Figure 2. The CT Scan of Patient's Head Sagittal and Coronal View

The patient's condition deteriorated the following day because GCS decreased and FH remained being longer but for PPT it dropped to 2x normal while APTT but 4x normal so

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being referred to Dr. Soetomo General Hospital was further examined found an abnormality in the form of FVIII which was so low that hemophilia A was diagnosed in this patient while waiting for the results of the FVIII examination to be given FFP because there was an extension of the FH both PPT and APTT while preparing for the surgery. In this patient after entering 1 unit of FFP (100 ml) there is an improvement in the physiology of hemostasis namely normal PPT and 2.5x normal APTT and when the results of measurement FVIII come out to indicate a hemophilia A disorder whose main therapy is given FVIII 1000 IU according to the FVIII target level calculation 100 IU / dL should be maintained at 500 IU / 12 hours according to the daily target of FVIII 50 IU / dL.

During surgery, the hemorrhage that occurs in patients can be controlled by the surgeon and after surgery, the patient is maintained FVIII for 14 days as recommended by WFH. And FVIII treatment of patients is given episodically, for example, if the bleeding occurs significantly because the availability of FVIII is difficult to obtain. But the condition of the patient from day to day is getting better and even consciousness begins to improve after 14 days post-surgery and 1 month later the patient gets back coagulation as an episodic handler.

DISCUSSION

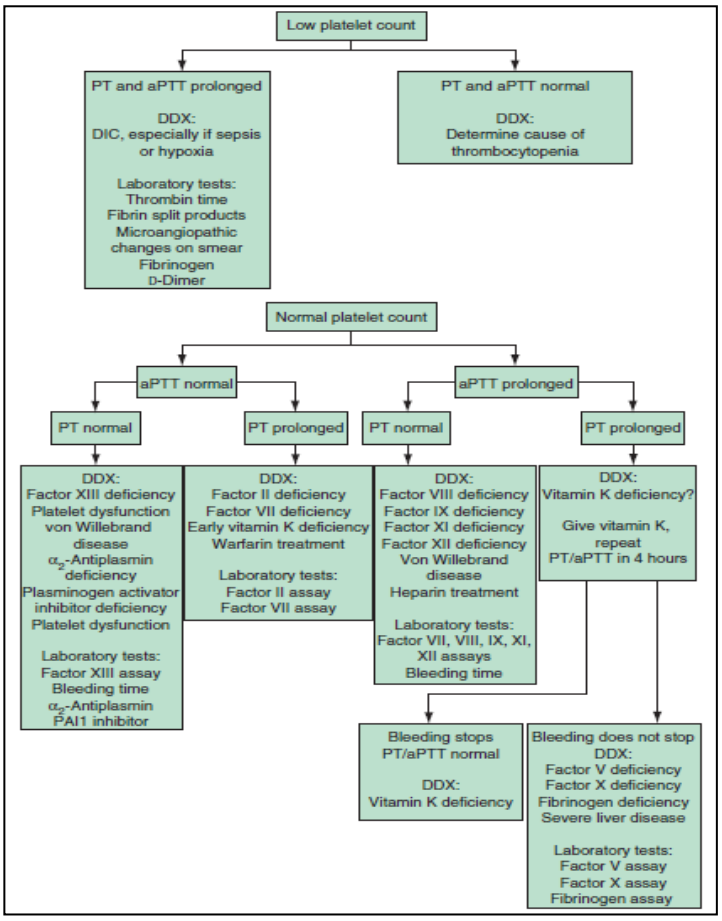

Figure 3. Differential Diagnosis of Bleeding Disorders (4)

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Initially, the patient experienced subdural hemorrhage due to blood clotting disorders in the form of vitamin K deficiency. (3) Because of PPT and aPTT were extended to 4 times normal without thrombocytopenia and after being given vitamin K treatment, PPT was repaired but the aPTT was extended so that deficiency factors were suspected. (3)(5)(6) Indicates the presence of severe factor VIII deficiency (1%) and upright diagnosis of Hemophilia A in this patient.

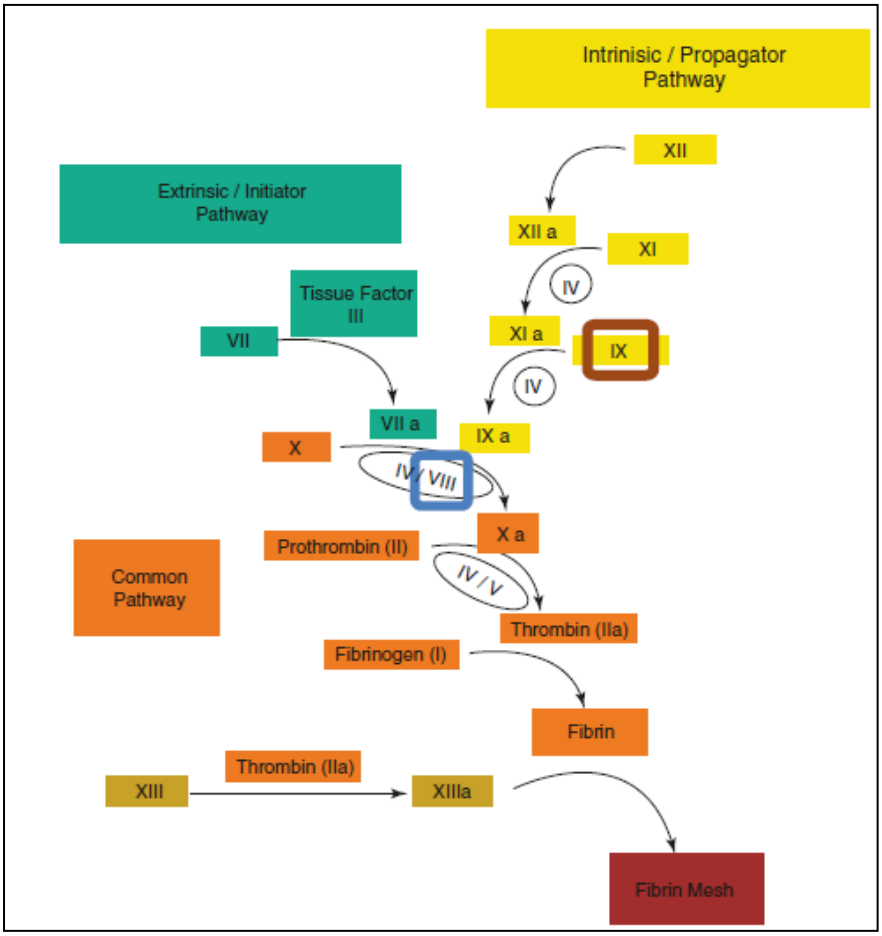

Figure 4. Coagulation Cascade (5)

Finally, the patient can be given FVIII treatment and undergo clot evacuation craniotomy with controlled hemorrhage.

FVIII Concentrate is the first-line treatment for hemophilia A. All plasma derivative products currently on the market are listed in the WFH Registry of Clotting Factor Concentrates. Consult with product inserts for specific details. (1)(2)

One bottle of factor concentrate is available in each dose ranging from 250 to 3000 units. In the absence of an inhibitor, each FVIII unit per kilogram of intravenous weight will increase plasma FVIII levels by about 2 IU / dl. Around 8 until 12 hours is the half-live of FVIII. Fifteen minutes after infusion to verify the dose, the patient factor level must be measured. The desired factor level in plasma (IU/dl) calculated by multiplying the patient's weight in kilograms by 0.5. (1)(2)

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Clotting factor number	Clotting factor name	Function	Plasma half-life (h)	Plasma concentration (mg/L)
I	Fibrinogen	Clot formation	90	3000
II	Prothrombin	Activation of I, V, VII, VIII, XI, XIII, protein C, platelets	65	100
III	TF	Co factor of VIIa	-	-
IV	Calcium	Facilitates coagulation factor binding to phospholipids	-	-
V	Proacclerin, labile factor	Co-factor of X-prothrombinase complex	15	10
VI	Unassigned			
VII	Stable factor, proconvertin	Activates factors IX, X	5	0.5
VIII	Antihaemophilic factor A	Co-factor of IX-tenase complex	10	0.1
IX	Antihaemophilic factor B or Christmas factor	Activates X: Forms tenase complex with factor VIII	25	5
X	Stuart-Prower factor	Prothrombinase complex with factor V: Activates factor II	40	10
XI	Plasma thromboplastin antecedent	Activates factor IX	45	5
XII	Hageman factor	Activates factor XI, VII and prekallikrein		-
XIII	Fibrin-stabilising factor	Crosslinks fibrin	200	30
XIV	Prekallikerin (F Fletcher)	Serine protease zymogen	35	
XV	HMWK- (F Fitzgerald)	Co factor	150	
XVI	vWf	Binds to VIII, mediates platelet adhesion	12	10 µg/mL
XVII	Antithrombin III	Inhibits IIa, Xa, and other proteases	72	0.15-0.2 mg/mL
XVIII	Heparin cofactor II	Inhibits IIa	60	-
XIX	Protein C	Inactivates Va and VIIIa	0.4	-
XX	Protein S	Cofactor for activated protein C		-

HMWK – High molecular weight kininogen; vWf – Von Willebrand factor; TF – Tissue factor

Figure 5. Table of Nomenclature of Coagulation Cascade (5)

Table 1. Expected peak levels of plasma FVIII and duration of administration in hemophilia A patients who have central nervous system bleeding

		Desired Level (IU/DL)	Duration (days)
No Significant Resource Constraint	**Initial**	80–100	1-7
	Maintenance	50	8 – 21
Significant Resource Constraint	**Initial**	50-80	1-3
	Maintenance	30-50	4-7
		20-40	8-14

For example: 20 kg × 100 (IU / dl desired level rises) × 0.5 = 1,000 units of FVIII. See Tables 1 and 2 for the recommended factor level and the duration of replacement needed based on the type of hemorrhage.

FVIII must be infused by slow IV injection with a speed not exceeding 3 ml for adults and 100 units per minute in children. Subsequent doses are ideally based on half of FVIII and recovery in individual patients for certain products. It is best to use all FVIII bottles after they are dissolved, although many products have been shown to have increased stability after being dissolved. (1)(2) Continuous infusion avoids peaks and troughs and is considered by some to be profitable and more comfortable. However, patients must often be monitored for pump device failure.

Table 2. Expected peak levels of plasma FVIII and duration of administration in hemophilia A patients who undergo major surgery

		Desired Level (IU/DL)	Duration (days)
No Significant Resource Constraint	**Initial**	80–100	
	Maintenance	60-80	1 – 3
		40-60	4-6
		30-50	7-14
Significant Resource Constraint	**Initial**	60-80	
	Maintenance	30-40	1-3
		20-30	4-6
		10-20	7-14

Continuous infusion decreases the amount of clotting factor concentrate used and can be more affordable for hemophilia sufferer. However, this affordable comparison hanging on the dosage used for continuous and intermittent bolus infusions. Doses for continuous infusion are adjusted based on

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factor tests and elimination calculations. Because FVIII concentrate with very high purity is stable in IV solution for at least 24-48 hours at room temperature with a potential loss of less than 10%, continuous infusion for the same number of hours is possible. (1)(2)

Other therapies

So far many therapies can be used to treat hemophilia but depend on the severity of the disease. The following are therapies that can be used to treat hemophilia with their respective limitations.

Fresh Frozen Plasma (FFP)

FFP contains all coagulation factors. FFP contains FIX which is used to treat hemophilia B in countries that cannot afford FIX concentrates derived from plasma. (1)(2) The dose is 1 ml FFP = 1 unit factor. But in Hemophilia A it is difficult to reach FVIII levels higher than 30 IU / dl with FFP alone. FIX levels above 25 IU / dl are difficult to achieve. The initial acceptable dose is 15-20 ml/kg.

Cryoprecipitate

Cryoprecipitate is obtained by liquefying FFP slowly at 4 ° C for 10-24 hours and found deposits that are insoluble and separated by centrifugation. Cryoprecipitate contains FVIII (about 3-5 IU / ml), VWF, fibrinogen, and FXIII but not FIX or FXI. The resulting supernatant is called cryo-poor plasma and contains factors VII, IX, X, and XI. The dosage is 1 cryoprecipitate bag made from one FFP unit (200-250ml) which can contain 70–80 FVIII units in volumes of 30–40 ml. (1)(2)

Desmopressin

Desmopressin (1-deamino-8-D-arginine vasopressin) is a vasopressin synthetic analog that increases plasma levels of FVIII and VWF. Desmopressin does not affect FIX. The intranasal desmopressin response is more varied and less predictable. Increase FVIII 3-6 times the baseline level for patients with mild hemophilia, and maybe moderate. (1)(2)

Desmopressin is not for pregnancy but can be used during labor and in the post-partum period in a normal pregnancy. This drug is contained of a high level of VWF, so it has to avoid for pre-eclampsia and eclampsia patients. (1)(2)

The advantage of desmopressin compared to plasma products is the cost and risk of transmission of viral infections. Controlling hemorrhage is associated with hemostasis disorders. The decision to use DDAVP is the initial concentration of FVIII, the improvement achieved, and the duration of treatment needed because it can only be used for patients with mild and possibly moderate hemophilia. (1)(2) Repeated use can cause a decrease in response (tachyphylaxis). The rapid infusion causes tachycardia, redness, tremors, and abdominal discomfort.

Dosage:

1. 4 µg / ml for use i.v.
2. 15 µg / ml for use i.v. and s.c.
3. 150 µg per 1time nasal spray for BW <40 Kg
4. Single-dose 0.3 µ g / kg BW, route i.v. or s.c. can increase FVIII 3-6 times.
5. Desmopressin i.v. diluted 50-100 ml of physiological saline and given by slow intravenous infusion for 20-30 minutes. The peak response is seen about 60 minutes after administration either intravenously or subcutaneously. (1)(2)

Water retention and hyponatremia probably can be caused by antidiuretic activity results. The given of repeated doses must be accompanied by the measurement of plasma osmolality or sodium concentration. Hyponatremia is rare. Contraindications to

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children less than 2 years increase the risk of cerebral edema due to water retention. There are reports of thrombosis (including myocardial infarction) after desmopressin infusion in patients prone to cardiovascular disease. (1)(2)

Tranexamic acid

Tranexamic acid is an anti-fibrinolytic agent which competitively inhibits plasminogen activation into plasmin. Promotes clot stability and can be used as an adjunct therapy to hemophilia and several other hemorrhage disorders. Regular administration of the single-use of tranexamic acid does not prevent the hemarthroses in hemophilia. It is important to control the hemorrhage from the skin and mucous surfaces (for example; oral bleeding, epistaxis, menorrhagia). (1)(2)

Dosage of administration:

1. oral tablets 3-4 times/day.

2. i.v. 2-3 times / day

Gastrointestinal disorders (nausea, vomiting, or diarrhea) infrequently happen as a side effect, but heal if the dose is reduced. The infusion should be slow because the rapid injection can cause dizziness and hypotension. (1)(2)

Tranexamic acid is usually specified for 7 days after tooth extraction to discourage postoperative hemorrhage. The dose of Tranexamic acid must be reduced if there was a kidney disorder. The reduction of the dose will highly avoid the accumulation of toxins. (1)(2)

In the treatment of hematuria, it prevents the dissolution of clots in the ureter which can cause serious obstructive uropathy. And on thoracic surgery causes the development of an insoluble hematoma. (1)(2)

CONCLUSION

Diagnosing the exact cause in patients who have intracranial hemorrhage provides appropriate management so that the patients could be helped. Good collaboration between anesthesiologist, neurosurgeons, and pediatrics will increase the probability of successful management of critical bleeding without major sequelae.

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Literature Review

SCREENING PROTOCOL OF PROPOFOL INFUSION SYNDROME

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ABSTRACT

Introduction: Propofol is often used as sedation for a long time in the ICU. The use is at risk of Propofol Infusion Syndrome (PRIS) which is characterized by arrhythmias or decreased heart function, metabolic acidosis, rhabdomyolysis, and acute renal failure. **Literature Review:** The pathophysiology of PRIS is due to a disturbance in cell metabolism which inhibits the transport of Free Fatty Acid (FFA) into cells and inhibits the mitochondrial respiration chain. The management of PRIS is supportive of every symptom that arises so that screening is needed as a treatment to reduce high mortality rates. Screening using creatine phosphokinase (CPK) and lactate is supporting data as an initial introduction for symptoms of PRIS. **Conclusion:** PRIS can occur if continuous administration of propofol > 4 mg / kg / hour. CPK levels> 5000 IU / L become a benchmark to stop propofol before the onset symptoms of PRIS. Implementation of screening protocol is very helpful for clinicians to reduce mortality in ICU due to the use of propofol.

Keywords: Propofol Infusion Syndrome; Screening Protocol; Intensive Care Unit

ABSTRAK

Pendahuluan: Propofol sering digunakan sebagai sedasi dalam jangka waktu lama di ICU. Penggunaan tersebut berisiko terjadinya Propofol Infusion Syndrome (PRIS) yang ditandai dengan aritmia atau penurunan fungsi jantung, asidosis metabolic, rhabdomyolisis dan gagal ginjal akut. **Review Literatur:** Patofisiologi PRIS dikarenakan gangguan metabolisme sel dimana menghambat transportasi Free Fatty Acid (FFA) ke dalam sel dan menghambat rantai respirasi mitokondria. Tatalaksana PRIS berpacu pada suportif dari setiap gejala yang timbul sehingga diperlukan skrining sebagai tatalaksana untuk menurunkan angka motralitas yang tinggi. Skrining menggunakan creatin phosphokinase (CPK) dan laktat menjadi data pendukung sebagai pengenalan awal gejala PRIS. **Kesimpulan:** PRIS dapat terjadi apabila pemberian propofol secara kontinu >4 mg/kg/jam. Kadar CPK > 5000 IU/L menjadi patokan dihentikannya penggunaan propofol sebelum munculnya gejala PRIS. Sehingga implementasi protocol skrining sangat membantu klinisi dalam menurunkan mortalitas di ICU akibat penggunaan propofol.

Kata Kunci: Propofol Infusion Syndrome; Protokol Skrining; Intensive Care Unit

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INTRODUCTION

Propofol is a drug that is often used in operating rooms and intensive care units. Introduced since 1970 and began to be modified with soybean oil and egg phospholipids as emulsification in 1986. (1) Propofol has a hypnotic sedative effect given during induction and maintenance during general anesthesia. (2) This drug is the first choice compared to other intravenous hypnotic sedation drugs due to rapid onset and short conscious recovery and minimal effects of the central nervous system. (2)

The mechanism of action from propofol by interacting allosterically at the g-aminobutyric acid (GABAA) receptor. GABA is an inhibitory neurotransmitter in the brain when inactive, hyperpolarization of the postsynaptic cell membrane occurs and inhibits the function of the postsynaptic nerve.

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(3) Also, propofol is capable of binding to several ion channels and receptors. Compared with inhalation anesthesia, propofol does not excite the spinal motor nerves. So immobility during the administration of propofol is not caused by depression of the spinal cord. (2)

Using propofol was also risky. In 1990, there were death reports from the continuous administration of propofol in children with upper respiratory infections. Some death cases as the beginning terminology of propofol infusion syndrome (PRIS). (4) PRIS is rare but has the potential to increase the rate of mortality. A study showed 153 cases reported from 1990 to 2014 found that 51 percent had died. (5)

The definition of PRIS until now still no clear boundary. Symptoms that can occur include cardiac arrhythmias, metabolic acidosis, rhabdomyolysis, and acute kidney failure. Where if there are two from four criteria after continuous administration of propofol and no other etiology causes the appearance of these symptoms. However, some researchers also discovered hepatomegaly and hyperlipidemia. (6) Initially, PRIS was not widely known by many clinicians, but since Cremer published his findings in the Lancet the clinicians began to pay attention to the incident. Cremer showed that continuous administration of propofol in patients with post-head trauma surgery. A total of 67 patients with mechanical ventilation in the ICU and propofol as the main sedation of whom 11 experienced PRIS and all reportedly died. (7) Strengthened by European policies that patients with rhabdomyolysis, metabolic acidosis, hyperkalemia, elevated levels of creatinine protein kinase (CPK), and heart failure after continuous administration of propofol it is advisable to immediately reduce or stop it. (8) Besides, the Food and Drug Administration (FDA) the United States in 2006 stated to be careful about giving propofol continuously for children as sedation for a long time. The FDA also recommends not giving propofol in doses exceeding 4 mg/kg/hour in pediatric patients. (9)

Various cases reported with a high mortality rate from PRIS make clinicians challenged to look boundaries in diagnosing PRIS. Specific therapies to restore side effects arising from propofol have not yet been found. Therapy is still limited to the management of each symptom that appears including hemodialysis in acute renal failure with metabolic acidosis, hyperkalemia, and rhabdomyolysis. However, this therapy indicates a state of delay in patients with PRIS. A PRIS prevention protocol is needed so that can decrease the number of PRIS events that have a positive impact on decreasing mortality. However, there is still little research and case reports that address the screening protocol. On this occasion, the author tries to discuss the diagnostic limits of PRIS, the latest therapies, and equally important screening of PRIS.

LITERATURE REVIEW

Propofol

Sedation drugs are widely used in the intensive care unit and operating rooms with a variety of routes intravenous administration both bolus repeatedly and continuously. In the past, benzodiazepines were the main drugs sedation in the ICU but recent studies and meta-analysis showed that nonbenzodiazepines such as propofol and dexmedetomidine had good results with fewer degrees of delirium and shorter use of ventilators. Besides, similar to benzodiazepines, propofol has no analgesic effect. (10)

Propofol is the structure of isopropyl phenol (2,6-diisopropyl phenol) which

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consists of 10% soybean oil, 2.25% glycerol, 1.2% egg phosphate, and 1% solvent solution. The content of soybean oil and egg lecithin is combined with long-chain triglycerides. This formulation is risk of bacterial growth and an increase in triglyceride levels when given continuously for a long time. Unlike thiopental, ketamine, and etomidate, propofol is a chiral compound. Mixing propofol with other drugs such as lidocaine is not recommended because the risk of pulmonary embolism. (11) People with egg allergy do not indicate that administration of propofol sedation is not permitted. In people with egg allergy, most of them are allergic to egg whites (egg albumin) not to egg lecithin derived from egg yolk.

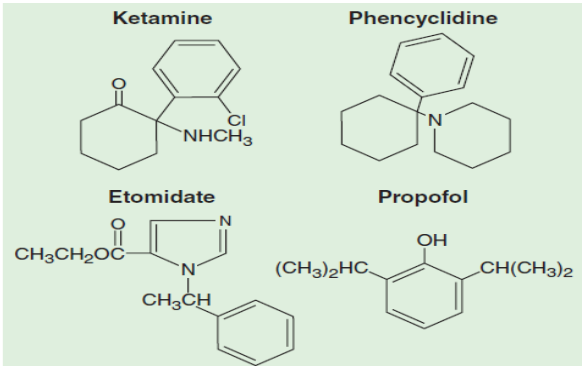

Figure 1. Structure of propofol chains compared with other groups sedative drugs (3)

G-aminobutyric acid (GABA) is an inhibitory neurotransmitter in the brain. We know propofol works selectively at the GABAA receptor. Interactions on GABAA receptors have a sedative-hypnotic effect. When activated at the receptor there is an increase conductance of the transmembrane chloride which results in hyperpolarization of the post synapse cell membrane and the post synapse nerve. (3)

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics of propofol is quite complex compared to other sedation drugs. We know that propofol only has intravenous preparations. Propofol has a fast onset of action because it is very fat-soluble which can penetrate the blood-brain barrier quickly and distributed quickly to the peripheral tissues. Propofol oxidation in the liver which binds with glucuronic acid into propofol-1-glucuronide, quinol-1- glucuronide, and quinol-4-glucuronide which all of them can be excreted in the kidneys. (12) Only a few propofol are excreted where <1% excretion in urine and 2% in feces. All of these are inactive metabolites because speed clearance of propofol is> 1.5 L / min over the blood flow in the liver. Also, extrahepatic metabolism also occurs in the kidneys. The kidneys have an important role in propofol excretion where 30% occur in the elderly. So that becomes an explanation of why propofol has a faster clearance time. The clinician's concern is that age-related doses in which 80-year-old patients only need 50% of propofol doses compared to 20-year-old patients to achieve the same level of hypnosis because it is related to decreased volume distribution in geriatric resulting in low drug clearance. In contrast to children aged> 3 years requires a dose based on body weight because volume distribution of child larger and clearance faster. (3)

Pharmacodynamics of propofol in the respiratory system can occur apnea due to depression from the hypoxic ventilator drive and inhibition of the normal response to hypercarbia. Compared with thiopental, propofol has a better effect in suppressing upper airway reflexes during the intubation process. Besides that compared to etomidate and barbiturate, propofol has a risk of histamine release but the incidence of asthma is lower compared to etomidate and barbiturate. (1) Cardiovascular effects are also a concern for the use of propofol were a decrease in mean arterial pressure (MAP) due

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to vasoconstrictor inhibition of the sympathetic nerves which ends a decrease in systemic vascular resistance (SVR). Be careful in older patients or with beta-blocker treatment which further worsens decrease MAP and decreased cardiac contractility. (3) Propofol can reduce Cerebral Metabolic Rate for Oxygen (CMRO2), Cerebral Blood Flow (CBF), and intracranial pressure. The hypotensive effect of giving propofol causes a decrease in CBF. Besides cerebral autoregulation in response to the decline in CBF is also disrupted. The decrease in CBF velocity is also related to changes in PaCO2 related to propofol administration. (13)

Clinically, propofol used for induction and maintenance of general anesthesia. The dose that can be given when induction is 1-2.5 mg/kg and will be increasingly adjusted to age, body mass index, and volume distribution. As for maintenance doses, it ranges from 50-150 µg/kg/min both combination with opiates and nitrogen. The best step in the induction process is by titration and monitoring of propofol administration. Both opiate and midazolam can change the concentration of propofol. A combination with alfentanil can reduce elimination clearance from 2.1 L / min to 1.9 L / min while midazolam from 1.94 L / min to 1.6 L / min. (14) Another use of propofol is sedation during administration of mechanical ventilation in ICU. The speed of continuous administration and the maximum number of doses must be considered during the administration of propofol. The speed of propofol administration under regional anesthesia is half that of general anesthesia at 30 µg/kg/min. Geriatric patients should be reduced by half their speed compared to young adults. Sedation speed with propofol is a maximum 80 µg/kg / min or <5mg/kg/hour. Plus special attention when the patient is also given a vasopressor or inotropic escalation dose. (15)

Non-hypnotic effects are also present in the administration of propofol including antiemetic, anti-pruritic, anti-convulsive, and decreased bronchoconstriction. Postoperative Nausea Vomiting (PONV) can be suppressed by administering a propofol sub hypnotic dose that is around 10-15 mg IV in the Post Anesthesia Care Unit (PACU). Sub hypnotic doses can also be given to patients with chemotherapy induce nausea vomit and are equally effective when compared with ondansetron drugs. (16) Anti-pruritus effects can also be given to patients with neuraxial opioids or cholestasis. The mechanism of this effect is by the way drugs able to suppress the activity of the spinal cord. The dose that can be given is 10 mg IV. Propofol also has an anti-convulsive effect that works in GABA mediated prescription and inhibition of chloride ions in postsynaptic. Doses that can be given to suppress seizures are> 1 mg/kg. Besides, propofol also minimizes bronchoconstriction during induction and intubation in patients with a history of asthma when compared with thiopental. (17)

Propofol Infusion Syndrome

Death report after the continuous administration of propofol occurred in 1990 in Denmark where it occurred in children aged 3 years. In 1992, it was reported that 5 children also died after continuous administration of propofol. This is similar to the clinical symptoms that appeared with Danish's incident report in 1990. Terminology Propofol Infusion Syndrome (PRIS) was introduced by Bray who made observations of 18 cases of PRIS that occur in children. (18) PRIS did not only occur in pediatric patients, Cremer's case report in The Lancet where there were 18 cases of death with PRIS in post neurosurgical

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patients in ICU with mechanical ventilation. There are also cases of women in 30 years with acute exacerbation of bronchial asthma who have lactic acidosis and anion gap metabolic acidosis whose causes cannot be explained after receiving propofol therapy continuously for 2 hours with mechanical ventilation. (7)

PRIS definition is indeed difficult to determine because of the combination of too many case variations. So that the explanation of the collection of symptoms includes metabolic acidosis with no clear cause, rhabdomyolysis, hyperkalemia, hepatomegaly, kidney failure, hyperlipidemia, arrhythmias, and progressive heart failure. However, Bray makes it easy by dividing into 4 major components consist of:

1. Cardiac arrhythmia or heart failure
2. Metabolic acidosis
3. Rhabdomyolysis
4. Acute Kidney Failure

If there are two sets of symptoms from the 4 indicators after continuous administration of propofol by excluding the other etiology causing the symptoms mentioned above. (19)

Pathophysiology of PRIS

Normally glucose becomes the main energy in various systems in our body. However, during the process of fasting and critical illness, there is a change in the source of energy where Free Fatty Acids (FFA) are the source of energy. This change in energy source is activated by various stress hormones such as epinephrine and cortisol which are able to modulate the activity of lipase in fat tissue. Lipase activity degrades triglycerides into glycerol and FFA where glycerol is a source of glucose and FFA as a source of beta-oxidation in mitochondria. (20)

In PRIS conditions, there are 2 conditions where propofol can inhibit the formation of intracellular energy, namely by inhibiting the transport of FFA into cells and inhibition of the mitochondrial respiratory chain. Let's try to discuss this in detail. Propofol is able to inhibit FFA transportation into cells. The rule of the FFA is changed to acyl-CoA by CoA synthase. Acyl Co-A will bind to Carnitine palmitoyltransferase-I which is outside the mitochondrial membrane to acylcarnitine. acylcarnitine will enter the mitochondrial membrane by binding to carnitine palmitoyltransferase-II to carnitine. Propofol itself in this mechanism prevents acyl-coA bonding with carnitine palmitoyltransferase-I. (21)

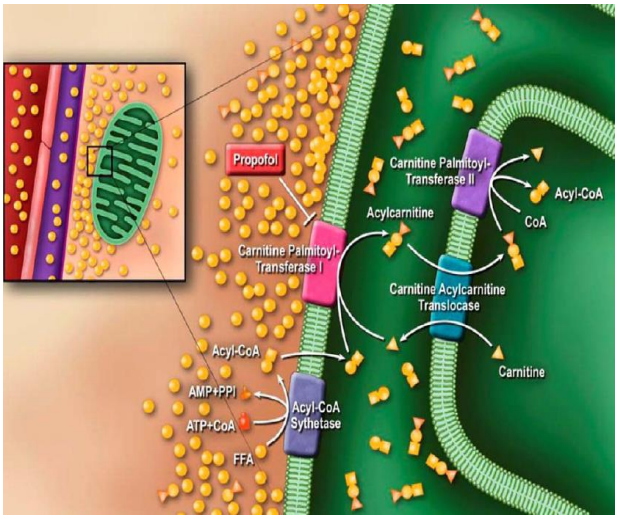

Figure 2. Pathogenesis Propofol Inhibits Transport of FFA into Cells (32)

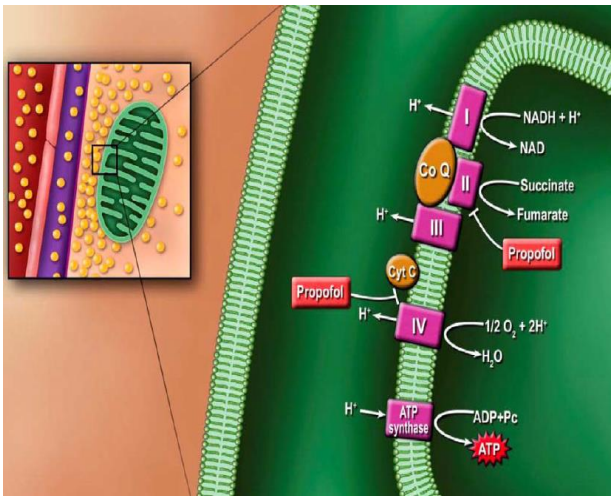

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Figure 3. Pathogenesis Propofol Inhibits Mitochondrial Respiration Chain (32)

Besides that, propofol can inhibit the mitochondrial respiration chain. Normally there are 4 complex components in the respiration chain. The first complex starts from electrons passing through nicotinamide adenine dinucleotide (NADH) to coenzyme Q (CoQ). the second complex of succinate becomes fumarate with the help of CoQ. The third complex CoQ becomes Cytochrome c (Cyt C). the fourth complex of Cyt C becomes cytochrome c oxidase. These four processes move hydrogen ions into the intermembrane space to produce ATP energy. Propofol itself is able to inhibit processes in complexes two and four. (22)

Clinical Manifestations

Organ systems involved in PRIS include cardiovascular, liver, renal, musculoskeletal, and metabolic. In the cardiovascular system wherein the initial phase there are tachycardia and hypotension but if the condition becomes more severe it becomes bradycardia with widening QRS complexes such as Brugada like rhythm. This is due to the antagonistic response of calcium channels and beta-adrenergic receptors. If it becomes more severe, it will become ventricular fibrillation to asystole. (23) The effect of propofol also affects liver function where there is an increase in transaminases and bilirubin. On physical examination, there can be hepatomegaly. Besides, increases in serum triglycerides and cholesterol are due to kinetic lipid disorders where hepatocellular necrosis previously occurred. (24)

In PRIS often occurs Acute Kidney Injury (AKI) which is marked with greenish-red urine color. The change of urine color is due to propofol metabolism in urine and increase phenol and uric acid. Although propofol is not nephrotoxic, it is damage to the kidneys due to secondary effects of rhabdomyolysis and myoglobin toxicity. (25) Rhabdomyolysis is the most common clinical manifestation of PRIS after decreased cardiovascular function. In rhabdomyolysis there is a decrease in ATP production and an increase in cell metabolic requirements resulting in muscle cytolysis followed by degradation of muscle products such as potassium, creatinine kinase, and myoglobin. (26) Betrosian says patients who are sedated with propofol for a long time can develop muscle necrosis without either followed by hemodynamic disorders. as well as other clinical symptoms of PRIS.(27) In critically ill patients, increased lactate can occur in decreased tissue perfusion, sepsis, and liver disorders which need to be a concern in establishing the diagnosis of PRIS after excluding these other causes. However, in its development, lactate examination is an early marker of the occurrence of PRIS so that it helps clinically in establishing PRIS. (28)

Prevention

As a clinician, it is demanded to always be aware of the worst thing that can happen from every drug administration. The best measurement in the prevention of PRIS is vigilance by assuming suspicion that PRIS occurs in any propofol administration over a long period time. Based on some previous reports on the population of children treated in ICU with the administration of propofol sedation occurred PRIS. (21) Based on the pathophysiology, PRIS in children can occur because children have limited carbohydrate reserves so that they can be reduced more rapidly when in critical illness. This is certainly different when compared to adults who have more carbohydrate reserves. So it is

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advisable to avoid using prolonged use of propofol in children. (24)

In previous studies the risk of PRIS if propofol administration exceeds 4 mg/kg/hour or 67 mcg/kg/minute with a minimum of 48 hours of administration. This is reinforced by Cremer et al, where any increase in the administration of propofol 1 mg/kg/hour over a dose of 5 mg/kg / hour can increase the PRIS 1.93 times. (7) The provision of propofol can increase FFA levels by various mechanisms previously described. Clinicians must be vigilant when having patients with low carbohydrate reserves and increased fat administration. Also, patients with catecholamine or steroid therapy are also of concern given the high risk of PRIS. (29)

Diagnosis

Diagnosis of PRIS is still difficult because the clinical symptoms that appear are not typical and some symptoms are similar to other diseases such as sepsis. The main point is when giving propofol more than 4 mg/kg/hour or 67 mcg/kg/minute and or in more than 48 hours. Which appears one or more symptoms of arrhythmia or decreased heart function, metabolic acidosis, rhabdomyolysis, and kidney failure. Clinicians should consider stopping the administration of propofol if heart block or arrhythmia is found. (19)

Therapy

Some of the explanations mentioned above make clinicians must be careful when finding PRIS. Prevention of PRIS is the best choice compared to providing therapy because the mortality rate is quite high. Clinicians should not exceed the dose of propofol> 4 mg/kg/hour or > 67 mcg/kg/minute. Until now there has been no specific treatment or antidote from PRIS where management is only supportive of each symptom that arises. (19)

The first therapy when a PRIS is suspected is to stop giving propofol immediately. If you still need sedation then replace it with other drugs. Hyperkalemia can be treated by the administration of calcium gluconate with insulin and dextrose. (30) Besides, the management of metabolic acidosis with hyperkalemia and rhabdomyolysis is an indication of hemodialysis. PRIS is also widely reported in cases with traumatic brain injuries that require propofol for a long time. So that adequate fluid therapy reaches euvolemia is also noteworthy. Bradyarrhythmias causing cardiogenic shock require inotropic therapy or vasopressors such as norepinephrine and dobutamine. However, we know that the pharmacology of propofol also inhibits cardiac calcium blockers and beta receptors. So that administration of drugs that are similar in performance to catecholamines is less effective. (31) If bradyarrhythmias are refractory then consider a pacemaker. No less important is the comprehensive handling of patients in the ICU such as prevent the occurrence of ventilator-associated pneumonia, deep venous thrombosis prophylaxis, stress ulcer prophylaxis and the provision of adequate nutrition, in this case, is the provision of carbohydrates. (8)

Screening Protocol

PRIS screening approach began by looking for various markers which became supporting data for the early recognition of PRIS symptoms. The daily screening protocol of PRIS uses Creatine Phosphokinase (CPK) and lactate during the continuous use of propofol. This protocol has been started since 2006 and is still being worked on until now. Propofol is stopped when CPK reaches levels>

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5000 IU / L or Lactate> 4 mmol / L. Schroepel et al's study attempted to implement a screening protocol in the ICU with trauma cases. In 207 patients who received propofol continuously were divided into two phases. The first phase is patients who enter the PRIS criteria where cardiac arrhythmias occur, metabolic acidosis, rhabdomylysis, and acute kidney failure. The second phase is to impose CPK and lactate screening protocols on the continuous administration of propofol. Significant results were obtained where the PRIS group had high CPK and lactate levels. But not very significant in screening using lactate. (19) The Society of Critical Care Medicine (SCCM) recommends that for monitoring the occurrence of PRIS when continuous use of propofol. This was stated in the Guidelines of Pain, Agitation / Sedation, Delirium, Immobility and Sleep Disruption. (10)

The mechanism for PRIS is very complex with a mortality rate of up to 51%. Several studies have shown an extended length of stay (LOS) in the ICU and the use of ventilators in the ICU in patients with PRIS. So that it remains the best step is the prevention of PRIS by using CPK and lactate screening protocols. In addition, administration of propofol does not exceed 4 mg/kg/hour and if there is a PRIS, the treatment of each symptom must be adequate.

CONCLUSION

PRIS can occur in critically ill patients with propofol continuously exceeding 4 mg/kg/hour or 67 mcg/kg/minute. PRIS screening protocol using CPK> 5000 IU/L can be an initial marker choice to immediately stop giving propofol. The implementation of this screening protocol can be beneficial for prolonged administration of propofol sedation in the ICU.

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Conflict of Interest

There is no conflict of interest in this article writing process.

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3. *Homepage/Web site*

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