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ORIGINAL STUDY

The immune response to long-term administration of Dipravan compare to dormicum in surgical care unit

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Abstract

Introduction: **Immune response may be affected by anesthesia and sedation. In anesthesia, the immune response is temporary as anesthesia is used for short time. However, the immune response more obvious in critical illness patients because of the long time of sedation. Diprivan and dormicum are two commonly used medications for sedation and analgesia in critical care unit patients. Dipravan is a good medication for sedation in the surgical care unit. Dormicum in the surgical care unit, usually producing prolonged time of sedation when used for a long time in the surgical care unit.**

Patients and methods: **This article was done on 60 patients undergoing vascular and abdominal operation who were to use sedation for a long time more than one day postoperative. Patients were divided to one of two classes (each class = 30 0ne). class A. Patients use diprivan classs B. Patients use dormicum.**

Results: **No significant variation between both classes as regard age, sex, weight, surgical diagnosis, sedation score, ventilation and PO_2 with significant decrease in PH and PCO_2 in class B. Concerning heart rate and mean blood pressure there were a significant decrease in class B. As regard the immune response of serum tumor necrosis factor-α and interferon-γ and C-reactive protein showed significant increase in class A 24 h postinfusion, while no significant change in group B.**

Conclusion: **After 24 h continuous infusion, propofol stimulated, the production of the proinflammatory cytokines TNF- α, C-reactive protein and interferon-γ. While dormicum failed to do so.**

Keywords: Diprivan, Dormicum, Immune response

1. Introduction

The disturbance of immune response to anesthesia is unclear otherwise, the immune response of some anaesthetic and sedative medications are new well recognized [1]. The immune response to anesthesia is temporary as the anesthesia is used for a short timeotherwise, diprivan and dormicum are commenally used for sedation in critical care patients. Their immune response were more apparently when used for long times in critical care unit patients with impairment immune functions because sever infection, multitrauma, malginancy, or immune deficiency syndromes. The chemical mediators of the immune response, including the following, Interleukin-1 (IL-1), tumour necrosis factor-α (TNF-α), interferon-γ (IFN - γ), interleukin-6 (IL-6), and interleukin-8 (IL-8), which have general and local effects, which play important role in tissue damage, flaring of infection and tissue regeneration and healing [2]. The cytokines, interferon-γ (IFN-γ) is a good stimulant for T-lymphocyte. T-lymphocyte stimulate cell-mediated immunity [3]. Disturbance in inflammatory and proinflammatory cytokines play an important role in the pathophysiology of septicemia, septic shock acute lung injury (ALI), multiple organ dysfunction syndrome (MODS), trauma and malignancy [4]. Malignancy and major tissue trauma causing disturbance in T cell function and lead to impaired production of IFN-γ [5]. The literature

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describes a variety of in vitro studies comparing the effect of diprivan and dormicum on the immunomodulatory response. diprivan has been found to induce a market production in IFN-γ than dormicum and other intravenous anesthesia [6]. In the study of O'Donnell et al. [7], diprivan produced more inhibition on neutrophil polarization in vitro when compared with equivalent concentrations of dormicum, otherwise *in vivo* dormicum not produce inhibition on neutrophil polarization at relevant concentrations. In the in vitro study of Rossano et al. [8]. Both propofol and midazolam stimulate the release of TNF from monocytes. Diprivan induce significant increase INF-γ from lymphocyte otherwise midazolam induce nonsignificant increase. Although in vitro studies had shown complex modulation of the immune response, clinically, this work is less to be done as in vitro. It is difficult to determine if the work in vitro relates to what happen clinically. Therefore, it would be interesting to investigate the possibility of using cytokines as early markers to predict the immune status of the patients. It is important to determine the effect, if any, of diprivan and dormicum on the immune response is necessary in order to choose the ideal medication for sedation in critically ill patients for a long time, as regard the patient's immunity and the response to septicemia.

2. Patients and methods

This clinical study was performed on ICU patients in diabetic and endocrinology institute from April 2018 to March 2022. After approval by the Local Ethical Committee, an informed consent was obtained from each patient or his relatives. **Inclusion criteria**:- 60 patients who were planned for vascular and abdominal surgery whose received long-time sedation in critical care unit for more than 1 day. **Exclusion criteria**:- patients with history of convulsion or drug mal abuse, patients with impairment in their immunity, marked overweigth, renal or hepatic disorders and patients receiving corticosteroids or cytotoxic drugs. Patients were divided into one of two classes.

2.1. Class A: Diprivan class

Patients were given I.V. sedation with diprivan; loading dose of 1.5–2 mg/kg then continuous administration at a rate of 0.5–1.5 mg/kg/h.

2.2. Class B: Dormicum group

Patients received IV sedation with dormicum in the dose of 0.05–0.08 mg/kg then continuous administration in dose of 0.02–0.06 mg kg^{-1}/h^{-1}.

The 60 patients were be given IV analgesia in form of fentanyl in dose of (0.25–0.5 μg kg^{-1} h^{-1}). The doses of diprivan, dormicum and fentanyl were be recorded every hour.

2.2.1. Monitoring

The usual clinical variables and vital signs were monitored throughout the study, including cardiovascular, respiratory. Signs of stress response including hypertension, tachycardia were documented and dealt with by increasing the dose of the sedative. The duration of intubation and artificial ventilation were recorded. Also, sedation was assessed every 6 h to test the effectiveness of sedation and if it is insufficient, the dose of the sedation was increased. The sedation score: scaled an a three scale; 1 = asleep, 2 = drowsy or 3 = awake.

2.2.2. Laboratory investigations

Central venous blood samples (10 ml) from all tested patients drawn into heparinized syringes. The following parameters were measured in the collected plasma of the patients.

(1) Tumour Necrosis Factor-α (TNF-α).
(2) interferon-γ (IFN-γ).
(3) C- reactive protein (CRP).

Blood samples were drawn:

(1) Immediately prior to the start of IV sedation.
(2) 24 h from the start of treatment.

Blood samples were collected for arterial blood gases and routin laboratory assessment.

3. The aim of study

The aim of this article to investigate the immunomodulatory effects by measuring the cytokine and C-reactive protein in ICU patients as early markers of immunomodulatory effects to continous IV administration for 24 h of diprivan and dormicum.

Table 1. Age, weight, sex and surgical diagnosis, values are given as mean (SD) or median [range].

	class A (30 patients)	class B (30 patients)
Age; years	36 (7)	30 (9)
Weight; kg	77 (9)	79 (12)
Male:Female ratio	25/5	23/7
Surgical diagnosis:-		
1-Vascular surgery	22	18
2-Abdominal surgery	8	12

Table 2. Sedative scale in both groups. Values are median [range].

	class A (30 patients)	class B (30 patients)
Before infusion	3 [2–3]	3 [1–3]
After 6 h	2 [1–2]	2 [1–2]
After 12 h	2 [1–2]	2 [1–2]
After 18 h	2 [1–2]	2 [1–2]
After 24 h	2 [1–2]	2 [1–2]

There were no significant differences between both groups.

Table 4. Changes in heart rate in both classes.

Time	Heart rate (bpm)	
	class A (30 patients)	class B (30 patients)
Before sedation	97 (16)	92 (12)
After 6 h	96 (16)	89 (13)
After 12 h	95 (15)	94 (9)
After 18 h	93 (13)	95 (9)
After 24 h	91 (13)	85 (7)*

Value are mean (SD) *$P < 0.05$ compared to the propofol group.

4. Results

This article was conducted on 60 patients who were to receive long-term sedation for more than 24 h. Patients were divided to one of two classes (each one = 30); class A and class B. There were no statistically significant varation between the two classes as regard age, sex, weight, and surgical diagnosis (Table 1).

As regard of sedative scale. There were no stastistical significant variation between both classes. In both classes (diprivan and dormicum classes) the degrees of sedation was assessed by using the sedative scale, perinfusion, 6 h, 12 h, 18 h, and 24 h after starting the infusion are shown in Table 2. There were no statistically significant changes between both classes before infusion, after 6, 12, 18, and 24 h.

As regard the respiratory parameters. In both groups (diprivan and dormicum classes), there were no statistically variation regarding patients who needed artificial ventilation where in the diprivan class, 4 patients were intubated and ventilated and in the dormicum class, 3 patients were intubated and ventilated. In the diprivan class, 13% of patients were intubated and ventilated, while 87% of patients were spontaneously breathing via a face mask with 40% oxygen. In the dormicum class, 10% of patients were intubated and ventilated, and 90% of patients were spontaneously breathing via a face mask with 40% oxygen, the variation between the two classes was not statistically significant. In the diprivan class, 50% of patients were intubated for 2 days and 50% of patients were intubated for 3 days. In the dormicum class 40% of patients were intubated for 1 day and 60% of patients were intubated for 3 days, there were no statistically significant changes between both classes. Pressure support ventilation mode (PSV) and continuous positive airway pressure (CPAP) were used for patients during their ventilatory support. **As regard arterial blood gases analysis.** There is significant decrease in **pH** in the dormicum class, 18 h from the start of the infusion ($P < 0.05$).

No significant varation were detected between both classes, before infusion, 6 h, 12 h and at the end of the infusion (Table 3).

As regards PCO_2, there was no significant variation before infusion between both classes. However, there were significant decreases in PCO_2 in the dormicum class, 6 h, 12 h, 18 h, and 24 h after infusion ($P < 0.05$) compared to the diprivan class. **As regards PO_2,** there were no significant variation between both classes, at the start of infusion, 6, 12, 18 and 24 h after infusion (Table 3).

As regard the heart rate, there were no statistically significant variation between both classes in heart rate at the start, 6 h, 12 h and 18 h after the start of infusion, but after 24 h of infusion there was a statistically significant decrease in heart rate in the dormicum compared to the diprivan group ($P < 0.05$) (Table 4).

As regards the mean blood pressure. There were significant variation between both classes before infusion, after 6 and 18 h. After 12 h from the start of infusion, there were a significant reduction in the mean blood pressure in the diprivan class ($P < 0.05$) compared to the dormicum class. Also there were a significant reduction in the mean blood pressure in the diprivan class after 24 h from the start of infusion ($P < 0.001$) compared to the dormicum class Table 5.

Table 3. pH, PCO2, and PO2 changes in both classes.

	group A (30 patients)			group B (30 patients)		
	pH	PCO_2 (mm Hg)	PO_2 (mm Hg)	pH	PCO_2 (mm Hg)	PO_2 (mm Hg)
Before infusion	7.40 (0.05)	36.03 (2.62)	102 (32)	7.38 (0.05)	35.03 (2.62)	90
After 6 h	7.38 (0.04)	35.13 (1.89)	101 (32)	7.39 (0.04)	34.13 (1.89)*	98.33 (24)
After 12 h	7.40 (0.04)	34.97 (1.73)	104 (31)	7.37 (0.04)	34 (1.68)*	3.93 (26)
After 18 h	7.39 (0.03)	34.33 (1.47)	98 (29)	7.38 (0.04)*	33.37 (1.54)*	93.9 (25)
After 24 h	7.39 (0.04)	34.97 (1.77)	100 (28)	7.39 (0.04)	33.93 (1.72)*	93.03 (26)

Values are mean (SD) *$P < 0.05$ compared to the propofol group.

Table 5. Change in mean blood pressure in both classes.

Time	Diprivan class (30 patients)	Dormicum class (30 patient)
	Mean BP (mm Hg)	Mean BP (mm Hg)
Before infusion	84 (10)	89 (8)
After 6 h	85 (7)	88 (6)
After 12 h	86 (5)**	90 (6)
After 18 h	89 (5)	90 (6)
After 24 h	76 (6)*	86 (6)

Values are mean (SD) *$P < 0.001$; **$P < 0.05$; +$P < 0.01$ compared to class B.

As regard of Preinfusion values of tumour necrosis factor-α (TNF-α), interferon-γ (IFN-γ) and C-reactive protein (CRP) were similar in both groups. Regarding TNF-α, after 24 h of long-term administration, diprivan caused a significant elevation in serum **TNF-α** from 11 (4 pg/ml) to 26 (8) pg/ml ($P < 0.001$ compared to the preinfusion level Table 6; there was no significant varation in TNF-α level in the class B Table 7. Concerning the **IFN-γ**, continuous diprivan infusion caused a significant increase in the **IFN-γ** level from 106 (4 pg/ml) to 135 (10) pg/ml ($P < 0.05$ in relation to preinfusion level), Table 6; where as in the group B, there was no significant changes in the **IFN-γ** levels, Table 7. **As regards the CRP**, diprivan infusion caused a significant increase in the post-infusion levels as compared to the preinfusion levels from 120 (25 pg/ml) to 144 (40) pg/ml) ($P < 0.001$ in relation to the preinfusion level) Table 6 whereas there was no significant varation in **CRP** level in the class B, Table 7.

5. Discussion

The diprivan is considered the good medication for sedation for patient in critical care unit when given by continuous intravenous [9]. Dormicum is producing prolonged sedation and drowness in the critical care unit patient, 0ccasionally when is given for long time by continuous intravenous [10] Anesthesia and sedation impaired the immunity function when given for long time by continuous intravenous in patient of critical care unit, this clinically important as it increase the risk of infection and help the flaring of infection at time of infection. Also, these sedative medications are commenally used in combination with analgesic agents which also impair the immune function when used for long time. **In our study**, after 24 h of prolonged intravenous administration, diprivan causes a statistically significant effect by increasing the proinflammatory cytokine (TNF-α) level otherwise dormicum had no significant effect on TNF-α. In Rossano et al. *in vivo* article [10], both diprivan and dormicum cause significant response of proinflammatory cytokines tumor necrosis factor (TNF) from monocytes. However, Larsen et al. [11] suggested that diprivan even in low dose casusing significant release of TNF from monocyte, otherwise dormicum did not induce this effect. In an article by Masahiko et al. [12], which studied the effect of anaesthesia and surgery on plasma cytokine levels, it was suggested that anaesthetic techniques are directed toward modulating adrenergic receptor stimulation (particularly α_2 receptors) and cytokine production [13]. Stimulation of α_2 adrenergic receptors can augment TNF production. Thus, it is reasonable to expect that general anaesthesia could affect cytokine production and release. The study of Zavala et al. [14] also suggested that dormicum, commenaly used for their sedative properties, attached to specific peripheral benzodiazepine receptor on monocyte and inhibit lipopolysaccharide – lead to up – regulation of both cyclooxygenase 2 and inducible nitric oxide lead to inhibation of TNF realase. In a study by Helen et al. [15], in that study, two groups of patients were studied, the first one received inhalational anaesthesia with isoflurane, while the second one, received intravenous anaesthesia with diprivan. As regard proinflammatory cytokine (TNF-α) production of no variation between both groups was detected.

In our study, after 24 h of prolonged intravenous administration, diprivan caused a significant varation in IFN-γ production, otherwise dormicum does not induce a significant varation in the level of IFN-

Table 6. Changes in cytokine levels and C-reactive protein in the class A (30 patients).

Cytokine	Preinfusion sample	Postinfusion sample
Tumour Necrosis Factor (pg/ml)	11 (4)	26 (8)**
Interferon-γ (pg/ml)	106 (4)	135 (10)*
C-reactive protein (pg/ml)	120 (25)	144 (40)**

Values are mean (SD), *$P < 0.05$, **$P < 0.001$ compared to the preinfusion level.

Table 7. Changes in cytokine levels and C-reactive protein in the class B (30 patients).

Cytokine	Preinfusion sample	Post-infusion sample
Tumour Necrosis Factor (pg/ml)	11 (4)	9 (4)
Interferon-γ (pg/ml)	104 (4)	101 (2)
C-reactive protein (pg/ml)	120 (22)	124 (24)

Values are mean (SD), no significant changes between preinfusion and postinfusion levels.

γ. Pirttikangas et al. [16,17], studied the effect of diprivan infusion as intravenous anaesthesia on the immune system in minor operations and they observed that increase in the number of T-lymphocyte in the patients under total intravenous anesthesia by diprivan otherwise this event not occure in inhalational with intravenous anesthesia. Diprivan has been found to stimulate excessive production of interleukein-1 alpha and interferon-gamma than other intravenous anesthesia [18] which may explain the difference. **In our study**, after 24 h of continuous infusion, in the diprivan class, there was a statistically significant increase of CRP in the postinfusion levels, whereas in the dormicum class, there was no statistically significant variation. In the study performed by Pirttikangas et al. [16,17], who study the effect of combined diprivan and isoflurane anaesthesia versus to total intravenous diprivan anesthesia upon the immunomodulatory response in patients undergoing abdominal operation; this study showed that both technique elevated C-reactive protein level which still increasing for several days after the operation. In this study, total intravenous diprivan infusion technique stimulate the cortisol production to the operation but had no effect on plasma C-reactive protein level compared with combined diprivan and isoflurane anaesthesia.

5.1. Conclusion

After 24 h continuous infusion, diprivan stimulated, the production of the proinflammatory cytokineTNF- α, C-reactive protein and interferon - γ. While dormicum failed to do so. It is important to choose a certain sedative that may have clinical implication in critical ill patients and in immuno − compromised patients.

Institutional Review Board (IRB) Approval Number

NHI000564.

Conflict of interest

There is no conflict of interest.

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