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Levomepromazine and Weaning From Sedation in Traumatic Brain Injured Patients.

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Abstract

Background: Sedation is a key for the management of patients with traumatic brain injuries. However, in some of the brain injured patients, weaning from sedation is a real challenge. In this work, we aim to evaluate the use of Levomepromazine as a safe strategy for weaning from sedation in mechanically ventilated brain injured patients.

Patients and Method: This is a prospective randomized controlled monocentric study carried out on patients admitted to the surgical ICU of the university hospital Ibn Rochd of Casablanca, between January 2022 and April 2022. The study included all mechanically ventilated patients over 18 years old admitted for traumatic brain injury. The patients were divided in two groups. The primary endpoint assessed was the need to resume sedation.

Results: In our study, the average age was 30 years ± 10.9. 97% were men. Resumption of sedation was 73.3% in the control group compared to only 37,5% in the group who took levomepromazine. Agitation was significantly lower in the levomepromazine group 18.7% compared to 73,3% in the control group. The reasons of re-sedation in both groups were accidental extubation due to the agitation of the patient and also patient-ventilator asynchrony. The length of stay was reduced in the control group with 18,4 days versus 28,7 days in the levomepromazine group. Concerning the impact on ICU deaths, there was no significant difference.

Conclusion: Levomepromazine has been shown through this work to reduce agitation in traumatic brain injured patients. ICU Death may not be influenced by the use of this molecule but it would reduce the need for prolonged or re-sedation.

Keywords: Levomepromazine, traumatic brain injury, Sedation, Weaning, Agitation, Re-sedation.

INTRODUCTION:

Sedation is a vital component of the management of patients with traumatic brain injuries, to minimize distress, pain and anxiety, and to facilitate mechanical ventilation. Maintaining the perfusion of the brain, its relaxation and its protection are fundamental objectives, the purpose of which is to avoid the extension of lesions and thus preserve the neuronal capital. Thus, using opioids and benzodiazepines is frequently required in the management of these patients.

Weaning from sedation-analgesia a pivotal stage between the acute and the resolving phase. A calm and progressive awakening is a guarantee of stability. It imposes a well conducted weaning. However, in some of the brain injured patients, weaning from sedation is a real challenge. In fact, prolonged or high-dose sedation with the drugs commonly used leads to tolerance, dependence, withdrawal, and delirium.

The literature on the use of neuroleptics in critically ill patients is scarce. Indeed, there is no standardized protocol regulating their use. Haloperidol is the only one that has been used for many years to manage agitation in ICU patients. Levomepromazin, also known as methotrimeprazine, is an old neuroleptic drug with an antipsychotic and strong sedative effect, commonly used as emergency drug in adult psychotic patients and for improving comfort in palliative care.

In this work, we aim to evaluate its use as a safe strategy for weaning from sedation in mechanically ventilated brain injured patients, while avoiding these deleterious side effects and minimize polypharmacy.

MATERIAL AND METHODS:

This is a prospective randomized controlled monocentric study carried out on patients admitted to the surgical ICU of the university hospital Ibn Rochd of Casablanca, between January 2022 and April 2022. The study included all mechanically ventilated patients over 18 years old admitted for traumatic brain injury. The patients were divided in two groups:

- **Group A:** with levomepromazine: Patients who received the neuroleptic since the start of sedation and continued until extubation and stabilization of the patient with a dosage of 25mg every 8 hours per day.
- **Group B:** group control, without levomepromazine: Patients who did not receive neuroleptic at any time during their hospital stay.

The duration of sedation for both groups was 48 hours. The primary endpoint assessed was the need to resume sedation. Success was defined as the absence of agitation without the resumption of sedation.

The secondary endpoints were the delirium on awakening, length of stay in the intensive care unit (days) and mortality.

RESULTS:

In our study, the average age was 30 years ± 10.9. 97% were men. 9 patients, which represents 29% of our population, are drug addicts. Among our patients, 15 had subdural hematoma, 7 had contusion, 7 others had subarachnoidal hemorrhage, and only 1 patient had an intraparenchymal hematoma (Table 1).

Table 1. Characteristics of patients enrolled in the study: comparison of the levomepromazine versus non-levomepromazine group

Variables	Group Levomepromazine (n=16)	Group control (n=15)	P -Value
Gender n (%) Male	16(53.3%)	13(46.7%)	0.27
Age (yo)	30 ±10.9	29.1±11.5	0.9

Medical history n (%) Hypertension	0	1(7.1%)	0.27
Drug users	4(25%)	5(35.7%)	0.52
Smokers	5(31.3%)	2(14.3%)	0.27
Duration of stay in the emergency n (%) ≤ 24 > 24	11(68.8%) 5(31,3%)	8(57.1%) 6(42.9%)	0.51
Type of injuries			0.4
Subdural hematoma	6(37.5%	9(64.3%)	
Contusion	5(31.3%)	2(14.3%)	
Subarachnoidal hemorrhage	4(25%)	3(21.4%)	
Intraparenchymal hematoma	1(6.3%)	0	

Resumption of sedation was 73.3% in the control group compared to only 37,5% in the group who took levomepromazine. Agitation was significantly lower in the levomepromazine group 18,7% compared to 73,3% in the control group. The reasons of re-sedation in both groups were accidental extubation due to the agitation of the patient and also patient-ventilator asynchrony (Table 2).

The length of stay was reduced in the control group with 18.4 days versus 28,7 days in the levomepromazine group. Concerning the impact on ICU deaths, there was no significant difference (Table 2).

Table 2. Outcomes : comparison of the levomepromazine versus non-levomepromazine group

Variables	**Group levomepromazine**	**Group control**	**P -Value**
Resumption of sedation	6 (37,5%)	11 (73.3%)	P=0,6
Agitation	3 (18,7%)	11(73,3%)	P=0.07
Length of stay in ICU (days)	28.7	18,4	**P<0.01***
Side effects	0	0	
Deaths	4 (25%)	5 (33,3%)	0.7

DISCUSSION:

In patients with difficult sedation, the escalation of standard analgo-sedatives (usually opiates and benzodiazepines) can lead to drug tolerance, dependence, and withdrawal. These agents may have significant side effects including delirium, agitation, hallucinations, unfavorable hemodynamics and even death, as described e.g. in the propofol infusion syndrome [1].

It is clearly necessary to treatment delirium rapidly, with a view to reducing the associated risk of early and late complications [2], and also to enable weaning from ventilation. Delirium and agitation exposes the patient to the risk of discontinuity of care (self-extubation, pulling out or disconnection of central lines, trauma). The risk of self-extubation with an inflated balloon is the most documented in the literature (2 to 13%), and the presence of agitation is one of the predictive factors in 48 to 78% of cases [2]. In fact, agitation was found in 45% of our population. No specific treatment is currently recommended for the management of delirium, largely due to a lack of efficacy data [3].

LMZ has the advantage of avoiding respiratory depression whilst being a potent sedative through its action on non-opioid, non-benzodiazepine receptors. Furthermore, it is an inexpensive agent that has antipsychotic, tranquilizing, and anxiolytic effects and is morphine-sparing [4]. It is also non-addictive thus avoiding tolerance, dependence and withdrawal [4].

Due to the long half-life of LMZ (approximately 20 hr), steady state plasma levels would only be achieved after 4 days at a constant dose and this lag time would be clinically unacceptable in these challenging patients. In order to achieve timely sedation control it was necessary in our strategy to rapidly escalate to adequate doses (25 mg per dose) [5,6].

To date, there have been no reports of intravenous administration of LMZ. The routes of administration recommended by the manufacturers and validated by the French agency for the safety of medicinal products (Agence Nationale de Sécurité du Médicament, ANSM), are the intramuscular and oral routes [6]. In our study, we only used oral LMZ.

In our study, we found that levomepromazine allowed an easier awakening with a better cooperation of the patient and a decrease in the incidence of agitation after the lightening of sedations in 81,3% of patients. The use of LMZ for the treatment of agitation in the ICU has never been reported in adults, but few series of pediatric patients described the use of LMZ by the oral route for refractory agitation or difficult sedation, with satisfactory results.

Snoek et al described in 2014 the successful use of LMZ as a strategy to manage difficult sedation by limiting prolonged highdose opioid or benzodiazepine use via enteral route, in seven critically ill children with refractory agitation despite haloperidol [7]. Their study showed the successful use of LMZ in anticipation of difficult sedation in patients with known behavioral problems including autism, who may otherwise require very high-dose conventional sedatives. They also found a temporal association between the commencement of LMZ, and the resolution of anxiety, discomfort and agitation [7].

Becerra et al have conducted an observational and longitudinal study in intensive care at Juan P. Garrahan Pediatric Hospital [8]. 36 patients older than 2 years were included. The average doses of levomepromazine was 0.38 mg/kg. 97% patients showed positive results. The regular sedative doses were reduced more than 20% after the use of LMZ. No adverse effects or deceased were registered [8].

The use of LMZ appears to be promising in the future. In fact, we found in our study that the mean length of stay in the ICU was significantly different between the LMZ group 28,7 days and control group 18,4 ; which is consistent with the literature as agitation leads to increased hospital length of stay and consequently hospital costs [2].

In 2021, Declercq and al reported their experience with the use of Levomepromazine (LMZ) for the treatment of delirium in patients treated for Acute Respiratory Distress Syndrome (ARDS) due to COVID-19. Out of 34 ARDS patients admitted from 22 March 2020 to 23 January 2021, 16 were treated with LMZ. The median time to initiation of LMZ was 6 days (interquartile, 5 to 8) from the start of sedation, and median duration of LMZ treatment was 5 (1 to 28) days. Of the 16 patients treated with LMZ, 12 were weaned from mechanical ventilation immediately following discontinuation, without recurrence of delirium. No adverse effects related to LMZ use were observed.

Based on these studies found in the literature, LMZ seems to be useful for the management of delirium occurring after lightening of sedation in patients regardless of the cause of admission, not only those with brain injury.

LIMITS:

Our original study has a few limitations, notably its mono-centric nature. Moreover, the absence of thresholds to define agitation, left to the appreciation of the clinician, probably leads to an overestimation of this effect of the latter.

CONCLUSION:

Levomepromazine has been shown through this work to reduce agitation in traumatic brain injured patients. ICU Death may not be influenced by the use of this molecule but it would reduce the need for prolonged or re-sedation, especially in the 15-30 age group and drug users, improve the management of patients in the intensive care unit, thus reducing hospital costs.

The challenge would be to elaborate a unique protocol for the use of levomepromazine, standardized for all the ICUs of our university hospital, in order to obtain a homogeneous use among the practitioners, allowing them to be more comfortable with this neuroleptic.

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Availability of data and materials :
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations Ethics approval :
The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

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Conflicts of interest :
There are no conflicts of interest.