Étude OB-Pain : douleur au décours d'une transplantation hépatique chez les patients atteints d'obésité par rapport aux patients non atteints d'obésité

Ambre Cuny

UNIVERSITE DE MONTPELLIER

FACULTE DE MEDECINE MONTPELLIER – NIMES

THESE

Pour obtenir le grade de

DOCTEUR EN MEDECINE

Présentée et soutenue publiquement

Par

Ambre CUNY

Le 19 octobre 2021

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" Étude OB-Pain : Douleur au décours d'une transplantation hépatique chez les patients atteints d'obésité par rapport aux patients non atteints d'obésité "

Directeur de thèse : Madame le Docteur Audrey DE JONG

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REMERCIEMENTS AUX MEMBRES DU JURY

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PLAN

OB-Pain : Pain management after liver transplantation in patients with obesity compared to patients without obesity

I. INTRODUCTION

A. Background

Orthotopic liver transplantation is the only curative treatment for acute or chronic end-stage liver failure of various causes [1, 2].

According to the latest figures from the French Biomedicine Agency, more than 1,300 liver transplants are performed in France within the 21 expert centers listed throughout the country. The number of liver transplants has been gradually increasing every year since 2012 with an annual growth of liver transplantation candidate by 8% [3].

The etiology of liver disease also evolved over the past years with an increasing prevalence of nonalcoholic fatty liver disease [4, 5]. Since 2014 in France, hepatocellular carcinoma became the main indication for liver transplantation, with a gradual decrease in viral etiologies such as hepatitis C due to the widespread use of direct antivirals [3].

In parallel to this ethological evolution, the prevalence of obesity in the population on the liver transplant waiting list is gradually increasing. These demographic data correlate with a constant increase in the prevalence of this disease, with an estimated 17% prevalence of obesity in France in 2019 [6].

Beyond the surgical expertise of this procedure, which requires trained teams in expert centers, the post-operative stay of the transplanted patient is often performed in intensive care units (ICUs) in order to prevent and treat immediate and differed complications related to the transplantation [7].

B. Postoperative pain management in liver transplantation

One of the main pillars of peri-operative management of liver transplantation is pain management.

Post-operative pain in liver transplantation has been investigated in small sample studies, comparing liver transplantation with two other abdominal surgeries: cholecystectomy [8] and liver resection [9]. These two clinical studies demonstrated lower morphine consumption for liver transplant patients in comparison with cholecystectomy and liver resection with comparable levels of analgesia.

The main analgesic protocols recommended multimodal analgesia, using nefopam and tramadol, to avoid the opioid-related side effects including excessive sedation and respiratory depression [10]. However, morphine remains a rescue therapy for uncontrolled pain.

In addition, a large-scale American study found that pre-liver transplantation opioid use has been associated with a 20%–50% higher risk of death and graft loss when compared with liver transplantation recipients without a history of opioid use before transplant [11].

All these data confirm the need for an anticipated and specific pain management protocol for liver transplant patients.

In our unit, all patients receive the same precise analgesia protocol, based on systematic use of nefopam and tramadol, and rescue morphine use in case of persistent pain [12].

Liver transplant patients, involving a single surgical model and a single analgesia protocol for all patients, represent a population of choice for comparing postoperative pain in specific groups of patients.

C. Care for a specific population: patients with obesity

Patients with obesity admitted in ICU present specific challenges due to the difficulties of caring for such patients, including positioning, transport, skin care, intravascular access, diagnostic imaging, and ventilator weaning [13-15].

During liver transplantation, obesity was associated with an higher risk of mortality, as shown in the results of the meta-analysis of Barone et al. in 2017 [16], and especially in patients with class III obesity, as also called "very severe" (i.e. with a BMI $\geq$ 40 kg/m^2).

These results were confirmed in other clinical studies reporting a higher risk of mortality in patients with obesity class II and III (i.e. with a BMI $\geq$ 35 kg/m^2) [17, 18].

It is worth noting that the definition of obesity remains large (i.e. BMI $\geq$ 30 kg/m^2) and that multiple classes can be distinguished within this pathogenic entity [19] with increased risks of mortality for classes II and III (i.e. BMI $\geq$ 35 kg/m^2).

In addition, obesity can affect pharmacokinetics (relationship between drug dose and concentrations in the body) as well as pharmacodynamics (the pharmacologic effect resulting from a drug's concentration). This is of potential major significance as most drugs including pain medications elicit a strong concentration-effect relationship and dosing regimens are developed without consideration of the pathophysiologic effects of critical illness or obesity on pharmacokinetics.

Thus the therapeutic margins in patients with obesity remain narrow with an unpredictable metabolism and particularly in the case of liver transplantation with the risk of graft dysfunction [19].

Despite all these specificities associated with obesity, no data are currently available about post-operative pain in patients with obesity after liver transplantation.

Some studies were performed in other surgeries. An experimental study compared sensory thresholds, pain thresholds and pain tolerance that were assessed between patients eligible for bariatric surgery and control patients without obesity [20]. Results described higher thresholds and

lower subjective ratings in patients with obesity, especially in areas with excess subcutaneous fat tissue.

Other studies support these findings with experimental data related to galanin receptors that may modulate pain thresholds [21], including the role of ß-endorphin [20] and the presence of exosomes from adipose-derived stem [22].

Finally, a recent study on Analgesia Nociception Index (ANI) for the assessment of pain in critically ill patients [23] highlighted higher ANI values in patients with obesity. ANI is an electrophysiological monitoring tool based on the spectral analysis of heart rate variability, which varies from 0 (minimal parasympathetic tone, maximal stress-response and pain) to 100 (maximal parasympathetic tone, minimal stress-response and pain). These results of higher ANI values in patients with obesity could be explained by an impaired regulation of the neurovegetative system [23], and also by higher pain thresholds in patients with obesity, as detailed above [20].

D. Main hypothesis and objective of the study

Based on literature data in favor of lower pain levels in patients with obesity, we hypothesized that patients with obesity had a lower rate of rescue morphine analgesic consumption [24] for comparable levels of analgesia compared to patients without obesity, after liver transplantation.

Thus, we aimed to compare the rate of patients with rescue morphine analgesic consumption during the seven post-operative days following liver transplantation between patients without obesity and patients with obesity.

II. MATERIALS and METHODS

A. Population

The study took place in the 16-bed medical-surgical ICU of St Eloi Hospital, a 660-bed teaching and referral facility of the University of Montpellier in France.

Patients eligible for a liver transplantation were subjected to a multidisciplinary validation involving gastro-enterologists, surgeons and ICU physicians to validate their registration on the transplantation waiting list. The allocation of grafts was defined at a national level via the biomedicine agency according to territorial organization, severity of the disease and immunological compatibility [3]. After a patient had been allocated a graft, the final validation was the responsibility of the local medical-surgical team. After each liver transplantation, the patient was systematically transferred to ICU.

We included all consecutive patients ≥ 18 years old with obesity with the following inclusion criteria: liver transplantation and post-operative stay in ICU.

Obesity was defined by a Body Mass Index (BMI) ≥ 30 kg/m² [25]. The weight was recorded at ICU admission, after intraoperative drainage of ascites.

Patients without obesity were selected by chronological matching [26]: for each liver transplant patient with obesity, the patient without obesity previously transplanted was included in the group without obesity.

The aim of this chronological matching was to be free of any temporality, including day of transplantation and medical and surgical team.

We obtained the approval from the ethics committee (Comité Local d'Ethique Recherche, agreement number: 198711) of the Montpellier University Hospital.

The need for informed consent was waived on the basis that the intervention was a quality improvement institutional project [27].

B. Pain management during liver transplantation

The post-operative analgesia protocol for liver transplantation in the ICU of Saint Eloi was based on an early and adapted multimodal analgesia favoring optimal conditions for extubating [12]. Two molecules, nefopam and tramadol, were systematically introduced to all patients at ICU admission:

- Nefopam: bolus of 20 mg followed by infusion of 120 mg/24h
- Tramadol: bolus of 100 mg followed by infusion between 300 and 600 mg/24h

Therapeutic adjustments or complete cessation of these drugs were left to the discretion of the clinician based on multi-daily clinical assessments, using pain scales measured by bedside nurses [12].

It should be noted that morphine was not routinely used in liver transplant patients. Morphine could be introduced as a second line treatment in case of uncontrolled pain [12].

The pain assessment scales used were the Numeric Rating Scale (NRS) and the Behaviour Pain Scale (BPS).

NRS is a self-assessment scale for pain in the communicative patient. It is the most suitable self-report scale for ICU patients with the lowest failure rate and is the one preferred by patients [12, 28]. The patient chooses a number from 0 “no pain” to 10 that best represents his pain: 0 is "no pain" where 10 is “the worst pain imaginable”.

BPS is used as the gold standard to measure pain in the population of ICU patients unable to communicate according to guidelines, especially in the sedated and mechanically ventilated patient [29, 30].

The BPS is composed of 3 criteria: facial expression, upper limbs and compliance with ventilation. Each parameter is scored from 1 to 4 by trained staff and results in a score between 3 and 12 [31].

The numerical values of NRS and BPS if NRS was not feasible were used to classify the pain intensity [12]:

- Moderate pain: NRS value between 4 and 6 inclusive and/or BPS value between 4 and 5 inclusive
- Severe pain: NRS value >6 and/or BPS value >5

C. Study design

We conducted a retrospective cohort study of prospectively collected data in the medical-surgical ICU of the University of Montpellier Saint Eloi Hospital between January 2010 and December 2020.

The cohort was divided into 2 groups, one group with obesity and one group without obesity. The group with obesity was then divided into 2 groups.

We defined two groups of patients with obesity, depending on the stage of obesity [25]:

- Obesity class I, known as moderate: including patients with a BMI between 30 kg/m² and 34.9 kg/m²
- Obesity class II and III, known as severe and very severe: including patients with a BMI ≥ 35 kg/m², gathering patients with severe obesity known as class II (BMI between 35 kg/m² and 39.9 kg/m²) and patients with very severe obesity known as class III (BMI ≥ 40 kg/m²)

The control group was composed of liver transplant patients without obesity and therefore with a BMI < 30 kg/m² [25].

The study design included two comparisons. First, the group with obesity was compared with the group without obesity. Then, the group with obesity class II and III was compared with the group without obesity.

D. Data collection

The data were prospectively recorded. The intraoperative anesthetic record was documented using a point-of-care perioperative clinical information system (eXacto, Mexis S.A., Belgium). These records were merged with a second database derived from the ICU management system (ICCA, Philips, France) [32].

Data assessment was carried out by members of the anesthetic and ICU team, and data were collected in a standardized manner.

For each patient the following data were collected:

- Demographic data: age, gender, weight, height, BMI
- History and comorbidities: alcohol consumption, arterial hypertension, diabetes, chronic renal failure, chronic pain
- Etiology of liver disease (nonalcoholic steatohepatitis, alcoholic liver disease, viral hepatitis B, viral hepatitis C, autoimmune hepatitis, fulminant hepatitis, liver retransplants, mixed and other) and staging cirrhosis by scores (Model for End-Stage Liver Disease MELD and Child-Pugh)
- Surgical procedure: active sepsis, ascites, anesthetic gas, opioid consumption, blood transfusion and norepinephrine consumption
- Simplified Acute Physiology Score II (SAPS II), complications (infection and revision surgery), length of ICU stay, mortality in ICU
- Mortality at Day-28

Regarding the stay in ICU, the follow-up was performed daily up to the first 7 days after the liver transplantation and include:

- Biological data: hemoglobin (g/dL), platelets (/mm^3), prothrombin (%) and factor V (%), aspartate transaminase AST (UI/L), alanine transaminase ALT (UI/L), bilirubin total and conjugated (µmol/L), serum albumin levels (g/L)
- Assessment of consciousness and pain: Richmond Agitation Sedation Scale (RASS) [33, 34], delirium according to the Confusion Assessment Method for the ICU (CAM-ICU)

[35], hepatic encephalopathy clinically defined as by alterations of personality, consciousness, cognition and motor function [36], NRS [12], BPS [12]

- Analgesic consumption [37]: molecules and dosing
- Immunosuppression: molecules and dosing
- Surgical drains and type (tubular, salem, biliary, other)

E. Endpoints

The primary endpoint was the rate of rescue morphine analgesic consumption during the first 7 days of ICU stay.

The secondary endpoints included:

- At least one episode of severe pain during the first 7 days of ICU stay, assessed daily until Day-7
- At least one episode of moderate pain during the first 7 days of ICU stay, assessed daily until Day-7
- At least one episode of severe or moderate pain during nursing-care during the first 7 days of ICU stay, assessed daily until Day-7
- Overall consumption of nefopam and tramadol during the first 7 days of ICU stay, in mg/kg of actual and ideal body weight, assessed daily until Day-7
- RASS levels assessed daily until Day-7
- At least one episode of delirium during the first 7 days of ICU stay, assessed daily until Day-7
- Number of surgical drains assessed daily until Day-7
- Liver biomarkers of graft recovery: prothrombin and factor V, AST, ALT, bilirubin total and conjugated assessed daily until Day-7
- Serum albumin levels assessed daily until Day-7
- Complications in ICU: revision surgery and sepsis
- Length of ICU stay
- Mortality in ICU and at Day-28

F. Statistical analysis

An incidence of 15% of the rescue morphine analgesic consumption was estimated in the post-operative management of liver transplantation in ICU. To show a 10% absolute reduction of the rate of rescue morphine analgesic consumption between groups (from 15% to 5%), we calculated that a number of patients per group of 70 would be needed for the trial to have 80% power to detect this difference with the use of a two-sided alpha level of 0.025 taking into account that two comparisons would be performed (group without obesity versus group with obesity, group without obesity versus group with obesity class II and III). Therefore, we chose to include at least 200 patients in the group without obesity and at least 200 patients in the group with obesity (at least 400 patients overall), estimating that it would allow to include at least 70 patients in the group with obesity class II and III.

Quantitative data were shown as mean and standard deviation or median and 25^{th}-75^{th} percentiles according to data distribution. Student't test (quantitative data) and chi-square test (qualitative data) were used between group.

As a patient could have several liver transplantations during his lifetime, each eligible stay was assessed independently.

First, the groups were compared regarding the primary endpoint (rate of patients with rescue morphine analgesic consumption) using a chi square test. Then, in case of significance in univariate analysis, to take into account baseline characteristics differences between the groups, a multivariate logistic regression was performed to provide adjusted results of the primary endpoint, considering *a priori* that etiology of cirrhosis, age, diabetes, sex and chronic pain would be confounding factors. These factors were entered into the multivariate model, and a final model including only significant variables was computed [27].

Second, the groups were compared regarding the secondary endpoints using a chi square test for qualitative endpoints (at least one episode of severe pain during the first 7 days of ICU stay assessed daily until Day-7, at least one episode of moderate pain during the first 7 days of ICU

stay assessed daily until Day-7, at least one episode of severe or moderate pain during nursing-care during the first 7 days of ICU stay assessed daily until Day-7, at least one episode of delirium during the first 7 days of ICU stay assessed daily until Day-7, complications in ICU: revision surgery and sepsis, and mortality in ICU and at Day-28) or a Student t test or Wilcoxon test for quantitative endpoints according to their distribution (RASS levels assessed daily until day-7, liver biomarkers of graft recovery: prothrombin and factor V, AST, ALT, bilirubin total and conjugated assessed daily until Day-7, serum albumin levels assessed daily until Day-7, number of surgical drains and length of ICU stay).

For patients with multiple stays for multiple liver transplants, the mortality analysis was done only on the first stay.

A generalized linear mixed-effects model for repeated measures taking into account the day as a random effect was performed to compare the overall consumption of nefopam and tramadol during the first 7 days of ICU stay, in mg/kg of actual and ideal body weight, assessed daily until Day-7.

A p-value of ≤ 0.025 was considered statistically significant, after Bonferroni correction for two comparisons (group without obesity versus group with obesity and group without obesity versus group with obesity class II and III).

The statistical analysis was performed by the Medical Statistical Department of the Montpellier University Hospital with the help of statistical software (SAS, version 9.4; SAS Institute; Cary, NC) [32].

III. RESULTS

During the study period, 718 patients had liver transplantation. We included all patients with obesity, which represent 212 patients (i.e. 29% of all the patients), and 212 patients without obesity by chronological matching. The patients with obesity were divided into two groups according to BMI: 142 patients with obesity class I and 70 patients with obesity class II and III. The flow chart of the study is shown in Figure 1. Among all the patients included, 7 patients were transplanted twice in our center: 3 patients without obesity, 2 patients with obesity class I and 2 patients with obesity class II and III.

Demographic and clinical characteristics are found in Table 1. Table 1A compared the group without obesity with the group with obesity. Table 1B compared the group without obesity and the group with obesity class II and III. Groups showed significant differences in age, comorbidities as well as in etiologies of cirrhosis.

There was no significant difference in the MELD and Child-Pugh scores on the day of transplantation, nor in SAPS II at the admission in ICU.

A. Primary endpoint

The rate of patients with rescue morphine analgesic consumption was 21% in the group without obesity (44 of 212 patients) and 14% in the group with obesity (29 of 212 patients, p=0.054, Figure 2A).

The rate of patients with rescue morphine analgesic consumption was significantly lower in the group with obesity class II and III (4 of 70 patients, 6%) than in the group without obesity (44 of 212 patients, 21%, p=0.0037, Figure 2B).

After adjustment on diabetes and alcoholism comorbidities, being in the group with obesity class II and III was still significantly associated with rescue morphine analgesic consumption (OR=3.43 (95% CI 1.17-10.1), p=0.025), in comparison with being in the group without obesity.

B. Secondary endpoints

There was no statistically significant difference between the group without obesity and the group with obesity, nor with the group with obesity class II and III, regarding the following secondary endpoints, assessed daily during the first 7 days of ICU stay: at least one episode of severe pain, at least one episode of moderate pain, at least one episode of severe or moderate pain during nursing-care (Table 2A and Table 2B) and RASS levels (Appendix 1A and 1B).

Analysis of consumption of nefopam (Figure 3A) and tramadol (Figure 4A) by actual body weight during the first 7 days in ICU showed significant differences between patients without obesity and patients with obesity, as with patients with obesity class II and III ($p < 0.001$).

However, when the comparisons of consumption of nefopam (Figure 3B) and tramadol (Figure 4B) were made by ideal body weight, there was no significant differences between patients without obesity and patients with obesity, nor with patients with obesity class II and III.

There was no statistically significant difference between patients with obesity and without obesity, nor with patients with obesity class II and III, regarding the number of surgical drains (Appendix 2A and 2B), the liver biomarkers of graft recovery and serum albumin levels (Appendix 3A and 3B), the complications in ICU, the length of ICU stay and the mortality in ICU and at Day-28 (Table 2A and 2B).

IV. DISCUSSION

In this study aiming to compare the rate of patients with rescue morphine analgesic consumption during the post-operative management of liver transplantation between patients with and without obesity, we have shown that the rate of patients with rescue morphine analgesic consumption was lower for patients with obesity class II and III when compared with patients without obesity.

Several mechanisms may explain these results. The first hypothesis is mechanical and has been suggested in experimental studies. Price et al. [20] compared sensory thresholds, pain thresholds and pain tolerance between patients with and without obesity. Their results described higher thresholds and lower subjective ratings in patients with obesity, especially in areas with excess subcutaneous fat. This could be explained by the stretching of the skin due to excess fat, which leads to a decrease in the density of the nerve fibers, and therefore the pain thresholds.

These results are supported by a more recent study evaluating the ability to assess pain of patients with obesity [38]. The assessment was performed comparatively between patients with and without obesity who received multiple random thermal and electrical stimuli on the skin, the intensity of which was between the pain threshold and tolerance. This study found that patients with severe obesity displayed hypoalgesia to noxious electrical stimuli together with difficulty in grading experimental noxious thermal and electrical stimuli in between pain threshold and tolerance.

The second hypothesis relates to an endocrine pattern with a favorable inflammatory environment. Adipose tissue is highly metabolically active, and visceral adipose tissue has a more deleterious adipocyte secretory profile resulting in insulin resistance and a chronic low-grade inflammatory and procoagulant state [19].

At the hormonal level, it has been shown that increased galanin levels and obesity are closely associated [21]. Galanin has an impact on the pain threshold through the activation of central GalR1 and peripheral GalR2. The increased galanin levels would lead to a modification of pain sensitivity in patients with obesity.

Other signaling pathways have also been described including the role of b-endorphin, an opioid neuropeptide produced by the pituitary gland involved in pain inhibition with increased concentration in patients with obesity [20, 39].

The last hypothesis still under study is a central dysregulation, including altered regulation of the neurovegetative system [23], associated with neuropsychological changes in patients with obesity [38].

These 3 mechanisms: mechanical, endocrine and dysregulation of the neurovegetative system, may explain an altered perception associated with lower perceived pain intensities in patients with severe obesity, leading to a decreased rescue morphine analgesic consumption (Figure 2B).

Whereas the rescue morphine analgesic consumption was reduced in patients with obesity class II and III, no difference was observed regarding the nefopam and tramadol consumption in relation to the ideal body weight. Pharmacokinetics of the molecules are altered during critical illness and further difficult to predict in patients with obesity [19]. This is of potential major significance as most drugs elicit a strong concentration-effect relationship and dosing regimens are developed without consideration of the pathophysiologic effects of critical illness or obesity on pharmacokinetics [40]. In the present study, the data suggest (Figures 3 and 4) that by adapting analgesic protocols to the ideal body weight, pain levels were comparable between patients without and with obesity (Table 2).

The results of the present study can have major impacts worldwide as anticipation of pain management is a priority considering the potentially impact of opioid use on the risk of death and graft loss [11, 41]. Reducing opioid prescription is particularly relevant in patients with obesity considering the increased risk of respiratory depression and sleep apnea in this population [42]. In the present study, the data suggest that opioid-sparing is possible during liver transplantation, with pain management protocols adapted to the ideal body weight.

Our study reinforces the experimental data about the potential protective effect of obesity on pain. The single surgical model and the use of a systematic analgesic protocol reduced many selection and confusion biases of observational studies [43].

This study has some limitations. The generalizability of the findings is limited because data were collected from one institution, and a retrospective design with chronological matching was used. However, the data were standardized and prospectively collected by the trained nurses and medical team and the chronological matching allowed to reduce the selections biases, ensuring a similar surgical and anesthetic team.

Several biases may interfere with the evaluation of pain: the use of high-dose corticosteroids, denervation of the transplanted organ, and liver dysfunction affecting the metabolism of the molecules used. Future studies are needed in different surgical and medical models to confirm these results. It would also be interesting in future studies to compare pain sites in order to assess the impact of obesity on the intensity and location of pain.

V. CONCLUSION

Patients with obesity class II and III had a lower rate of rescue morphine analgesic consumption following liver transplantation for comparable levels of analgesia, in comparison with patients without obesity. The application of a systemic analgesic protocol based on the ideal body weight appears to be the most suitable for patients with obesity in ICU.

VI. REFERENCES

1. Samuel D, Coilly A (2018) Management of patients with liver diseases on the waiting list for transplantation: a major impact to the success of liver transplantation. BMC medicine 16: 113

2. Bodzin AS, Baker TB (2018) Liver Transplantation Today: Where We Are Now and Where We Are Going. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 24: 1470-1475

3. Durand F, Antoine C, Soubrane O (2019) Liver Transplantation in France. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 25: 763-770

4. Parikh ND, Marrero WJ, Wang J, Steuer J, Tapper EB, Konerman M, Singal AG, Hutton DW, Byon E, Lavieri MS (2019) Projected increase in obesity and non-alcoholic-steatohepatitis-related liver transplantation waitlist additions in the United States. Hepatology (Baltimore, Md) 70: 487-495

5. Younossi ZM, Marchesini G, Pinto-Cortez H, Petta S (2019) Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis: Implications for Liver Transplantation. Transplantation 103: 22-27

6. Matta J, Carette C, Rives Lange C, Czernichow S (2018) [French and worldwide epidemiology of obesity]. Presse Med 47: 434-438

7. Jaber S, De Jong A (2019) 10 tips for intensive care management of transplanted liver patients. Intensive Care Med 45: 377-379

8. Eisenach JC, Plevak DJ, Van Dyke RA, Southorn PA, Danielson DR, Krom RA, Nagorney DM, Rettke SR (1989) Comparison of analgesic requirements after liver transplantation and cholecystectomy. Mayo Clinic proceedings 64: 356-359

9. Moretti EW, Robertson KM, Tuttle-Newhall JE, Clavien PA, Gan TJ (2002) Orthotopic liver transplant patients require less postoperative morphine than do patients undergoing hepatic resection. J Clin Anesth 14: 416-420

10. Feltracco P, Carollo C, Barbieri S, Milevoj M, Pettenuzzo T, Gringeri E, Boetto R, Ori C (2014) Pain control after liver transplantation surgery. Transplantation proceedings 46: 2300-2307

11. Randall HB, Alhamad T, Schnitzler MA, Zhang Z, Ford-Glanton S, Axelrod DA, Segev DL, Kasiske BL, Hess GP, Yuan H, Ouseph R, Lentine KL (2017) Survival implications of opioid use before and after liver transplantation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 23: 305-314

12. de Jong A, Molinari N, de Lattre S, Gniadek C, Carr J, Conseil M, Susbielles MP, Jung B, Jaber S, Chanques G (2013) Decreasing severe pain and serious adverse events while

moving intensive care unit patients: a prospective interventional study (the NURSE-DO project). Crit Care 17: R74

13. Pepin JL, Timsit JF, Tamisier R, Borel JC, Levy P, Jaber S (2016) Prevention and care of respiratory failure in obese patients. The Lancet Respiratory medicine 4: 407-418

14. De Jong A, Wrigge H, Hedenstierna G, Gattinoni L, Chiumello D, Frat JP, Ball L, Schetz M, Pickkers P, Jaber S (2020) How to ventilate obese patients in the ICU. Intensive Care Med 46: 2423-2435

15. De Jong A, Verzilli D, Sebbane M, Monnin M, Belafia F, Cisse M, Conseil M, Carr J, Jung B, Chanques G, Molinari N, Jaber S (2018) Medical Versus Surgical ICU Obese Patient Outcome: A Propensity-Matched Analysis to Resolve Clinical Trial Controversies. Crit Care Med 46: e294-e301

16. Barone M, Viggiani MT, Losurdo G, Principi M, Leandro G, Di Leo A (2017) Systematic review with meta-analysis: post-operative complications and mortality risk in liver transplant candidates with obesity. Alimentary pharmacology & therapeutics 46: 236-245

17. Triguero J, García A, Molina A, San Miguel C, Notario P, Villegas T, Becerra A, Expósito M, Muffak K, Álvarez MJ, Fundora Y (2015) Complications Associated With Liver Transplantation in Recipients With Body Mass Index >35 kg/m(2): Would It Be a Poor Prognosis Predictive Factor? Transplantation proceedings 47: 2650-2652

18. Molina Raya A, García Navarro A, San Miguel Méndez C, Domínguez Bastante M, Villegas Herrera MT, Granero K, Becerra Massare A, Villar Del Moral JM, Expósito M, Fundora Suárez Y (2016) Influence of Obesity on Liver Transplantation Outcomes. Transplantation proceedings 48: 2503-2505

19. Schetz M, De Jong A, Deane AM, Druml W, Hemelaar P, Pelosi P, Pickkers P, Reintam-Blaser A, Roberts J, Sakr Y, Jaber S (2019) Obesity in the critically ill: a narrative review. Intensive Care Med 45: 757-769

20. Price RC, Asenjo JF, Christou NV, Backman SB, Schweinhardt P (2013) The role of excess subcutaneous fat in pain and sensory sensitivity in obesity. European journal of pain (London, England) 17: 1316-1326

21. Yu M, Fang P, Shi M, Zhu Y, Sun Y, Li Q, Bo P, Zhang Z (2013) Galanin receptors possibly modulate the obesity-induced change in pain threshold. Peptides 44: 55-59

22. Zhao H, Shang Q, Pan Z, Bai Y, Li Z, Zhang H, Zhang Q, Guo C, Zhang L, Wang Q (2018) Exosomes From Adipose-Derived Stem Cells Attenuate Adipose Inflammation and Obesity Through Polarizing M2 Macrophages and Beiging in White Adipose Tissue. Diabetes 67: 235-247

23. Chanques G, Tarri T, Ride A, Prades A, De Jong A, Carr J, Molinari N, Jaber S (2017) Analgesia nociception index for the assessment of pain in critically ill patients: a diagnostic accuracy study. Br J Anaesth 119: 812-820

24. Lauretti GR, Oliveira GM, Pereira NL (2003) Comparison of sustained-release morphine with sustained-release oxycodone in advanced cancer patients. British journal of cancer 89: 2027-2030

25. OCDE, Santé Omdl (2020) Overweight and obesity.

26. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B (2000) Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 343: 332-336

27. De Jong A, Pouzeratte Y, Laplace A, Normanno M, Rollé A, Verzilli D, Perrigault PF, Colson P, Capdevila X, Molinari N, Jaber S (2021) Macintosh Videolaryngoscope for Intubation in the Operating Room: A Comparative Quality Improvement Project. Anesth Analg 132: 524-535

28. Chanques G, Viel E, Constantin JM, Jung B, de Lattre S, Carr J, Cisse M, Lefrant JY, Jaber S (2010) The measurement of pain in intensive care unit: comparison of 5 self-report intensity scales. Pain 151: 711-721

29. de Lattre S, de Jong A, Gniadek C, Carr J, Tondut G, Conseil M, Cissé M, Jaber S, Chanques G (2015) Douleur en réanimation : problématiques soignantes. Réanimation 24: 760-766

30. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BR, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R (2013) Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 41: 263-306

31. Payen JF, Bru O, Bosson JL, Lagrasta A, Novel E, Deschaux I, Lavagne P, Jacquot C (2001) Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 29: 2258-2263

32. De Jong A, Cossic J, Verzilli D, Monet C, Carr J, Conseil M, Monnin M, Cisse M, Belafia F, Molinari N, Chanques G, Jaber S (2018) Impact of the driving pressure on mortality in obese and non-obese ARDS patients: a retrospective study of 362 cases. Intensive Care Med 44: 1106-1114

33. Chanques G, Jaber S, Barbotte E, Verdier R, Henriette K, Lefrant JY, Eledjam JJ (2006) [Validation of the french translated Richmond vigilance-agitation scale]. Ann Fr Anesth Reanim 25: 696-701

34. Chanques G, Jaber S, Barbotte E, Violet S, Sebbane M, Perrigault PF, Mann C, Lefrant JY, Eledjam JJ (2006) Impact of systematic evaluation of pain and agitation in an intensive care unit. Crit Care Med 34: 1691-1699

35. Stollings JL, Kotfis K, Chanques G, Pun BT, Pandharipande PP, Ely EW (2021) Delirium in critical illness: clinical manifestations, outcomes, and management. Intensive Care Med 47: 1089-1103

36. Weissenborn K (2019) Hepatic Encephalopathy: Definition, Clinical Grading and Diagnostic Principles. Drugs 79: 5-9

37. Chanques G, Constantin JM, Devlin JW, Ely EW, Fraser GL, Gélinas C, Girard TD, Guérin C, Jabaudon M, Jaber S, Mehta S, Langer T, Murray MJ, Pandharipande P, Patel B, Payen JF, Puntillo K, Rochwerg B, Shehabi Y, Strøm T, Olsen HT, Kress JP (2020) Analgesia and sedation in patients with ARDS. Intensive Care Med 46: 2342-2356

38. Torensma B, Oudejans L, van Velzen M, Swank D, Niesters M, Dahan A (2017) Pain sensitivity and pain scoring in patients with morbid obesity. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery 13: 788-795

39. Xu F, Yin J, Xiong E, Wang R, Zhai J, Xie L, Li Y, Qin X, Wang E, Zhang Q, Zuo Y, Fan S, Wang S (2020) COMT gene variants and β-endorphin levels contribute to ethnic differences in experimental pain sensitivity. Molecular pain 16: 1744806920908474

40. Erstad BL, Barletta JF (2020) Drug dosing in the critically ill obese patient-a focus on sedation, analgesia, and delirium. Crit Care 24: 315

41. Braun HJ, Ascher NL (2021) Opioid Use and Liver Transplantation. Transplantation 105: 25-26

42. De Jong A, Rollé A, Souche FR, Yengui O, Verzilli D, Chanques G, Nocca D, Futier E, Jaber S (2020) How can I manage anaesthesia in obese patients? Anaesthesia, critical care & pain medicine 39: 229-238

43. de Jong A, Roca O, Guérin C (2020) COVID-19-related and non-COVID-related acute respiratory distress syndrome: two sides of the same coin? Intensive Care Med 46: 2197-2199

VII. TABLES

TABLE 1. Patient characteristics and medical characteristics.

Comparison between patients without obesity and patients with obesity (A), and comparison between patients without obesity and patients with obesity class II and III (B). Continuous data are expressed in median [25th-75th percentiles]. In case of missing data, the denominators are mentioned in the tables.

BMI, Body Mass Index; NASH, nonalcoholic steatohepatitis; SAPSII, Simplified Acute Physiology Score II; MELD, Model for End-Stage Liver Disease.

A. Patients without obesity and patients with obesity

	Patients without obesity n = 212	**Patients with obesity n = 212**	**p**
Age (years)	55 [47-62]	60 [54-65]	<0.001
Male Sex % (n)	149 (70%)	166 (78%)	0.059
BMI (kg/m^2)	25 [22-27]	32 [31-35]	<0.001
Medical background and comorbidities			
Alcohol consumption, n (%)	108 (51%)	145 (68%)	<0.001
Arterial hypertension, n (%)	52 (25%)	69 (33%)	0.067
Diabetes, n (%)	34 (16%)	68 (32%)	<0.001
Chronic renal failure, n (%)	39 (18%)	22 (10%)	0.019
Chronic pain, n (%)	30 (14%)	38 (18%)	0.29
Etiologies of Cirrhosis			
NASH, n (%)	9 (4%)	50 (24%)	<0.001
Alcoholic liver disease, n (%)	95 (45%)	137 (65%)	<0.001
Viral hepatitis B, n (%)	9 (4%)	9 (4%)	1
Viral hepatitis C, n (%)	46 (22%)	43 (20%)	0,72
Autoimmune hepatitis, n (%)	34 (16%)	14 (7%)	0.0022
Fulminant hepatitis, n (%)	9 (4%)	4 (2%)	0.16
Liver retransplants, n (%)	19 (9%)	7 (3%)	0.015
Mixed, n (%)	25 (12%)	50 (24)	0.0015
Other, n (%)	42 (20%)	14 (7%)	<0.001
Stage of cirrhosis			
Child-Pugh A, n (%)	40/195 (20%)	49/200 (25%)	0.55
Child-Pugh B, n (%)	49/195 (25%)	52/200 (26%)	
Child-Pugh C, n (%)	106/195 (55%)	99/200 (49%)	
SAPSII	37 [30-48]	38 [31-45]	0.97
MELD*	20 [12-28]	19 [13-28]	0.86

*: Missing data, analysis performed on 200 patients in the group patients without obesity and 182 patients in the group patients with obesity.

B. Patients without obesity and patients with obesity class II and III

	Patients without obesity n = 212	**Patients with obesity class II and III n = 70**	**p**
Age (years)	55 [47-62]	59 [51-64]	0.20
Male Sex % (n)	149 (70%)	54 (77%)	0.27
BMI (kg/m^2)	25 [22-27]	37 [35-39]	<0.001
Medical background and comorbidities			
Alcohol consumption, n (%)	108 (51%)	48 (69%)	0.010
Arterial Hypertension, n (%)	52 (25%)	25 (36%)	0.069
Diabetes, n (%)	34 (16%)	23 (33%)	0.0023
Chronic renal failure, n (%)	39 (18%)	7 (10%)	0.099
Chronic pain, n (%)	30 (14%)	8 (11%)	0.56
Etiologies of Cirrhosis			
NASH, n (%)	9 (4%)	24 (34%)	<0.001
Alcoholic liver disease, n (%)	95 (45%)	45 (64%)	0.0047
Viral hepatitis B, n (%)	9 (4%)	1 (1%)	0.46
Viral hepatitis C, n (%)	46 (22%)	14 (20%)	0.76
Autoimmune hepatitis, n (%)	34 (16%)	5 (7%)	0.062
Fulminant hepatitis, n (%)	9 (4%)	0 (0%)	0.080
Liver retransplants, n (%)	19 (9%)	2 (3%)	0.092
Mixed, n (%)	25 (12%)	20 (29%)	<0.001
Other, n (%)	42 (20%)	3 (4%)	0.0021
Stage of cirrhosis			
Child-Pugh A, n (%)	40/195 (20%)	16/63 (25%)	0.70
Child-Pugh B, n (%)	49/195 (25%)	14/63 (22%)	
Child-Pugh C, n (%)	106/195 (55%)	33/63 (53%)	
SAPSII	37 [30-48]	39 [31-49]	0.51
MELD*	20 [12-28]	18 [13-26]	0.46

*: Missing data, analysis performed on 200 patients in the group patients without obesity and 63 patients in the group patients with obesity class II and III.

TABLE 2. Secondary endpoints: analgesia, delirium, complications, length of stay and mortality.

Comparison of presence of at least one episode of severe pain during the first 7 days of ICU stay assessed daily until Day-7, at least one episode of moderate pain during the first 7 days of ICU stay assessed daily until Day-7, at least one episode of severe or moderate pain during nursing-care during the first 7 days of ICU stay assessed daily until Day-7, At least one episode of delirium during the first 7 days of ICU stay assessed daily until Day-7, complications in ICU: revision surgery and sepsis, length of ICU stay and mortality in ICU and at Day-28 between patients without obesity and patients with obesity (A), and between patients without obesity and patients with obesity class II and III (B). For patients with multiple stays for multiple liver transplants, the mortality analysis was done only on the first stay.

For patients with multiple stays for multiple liver transplants, the mortality analysis was done only on the first stay, i.e.: 209 patients in the group without obesity, 208 patients in the group with obesity and 68 patients in the group obesity class II and III (denominators are mentioned in the tables). Continuous data are expressed in median [25th-75th percentiles].

A. Patients without obesity and patients with obesity

	Patients without obesity n = 212	**Patients with obesity n = 212**	**p**
Analgesia and delirium assessment			
At least one episode of severe pain, n (%)	80 (38%)	75 (35%)	0.61
At least one episode of moderate pain, n (%)	127 (60%)	136 (64%)	0.38
At least one episode of severe or moderate pain during nursing care, n (%)	104 (49%)	109 (51%)	0.63
At least one episode of delirium, n (%)	48 (23%)	66 (31%)	0.049
Complications, length of stay and mortality			
Revision surgery, n (%)	65 (31%)	78 (37%)	0.18
Sepsis, n (%)	69 (33%)	90 (42%)	0.35
Length of ICU stay	11 [8-16]	11 [8-21]	0.63
Mortality in ICU, n/N (%)	11/209 (5%)	10/208 (5%)	0.84
Mortality at day 28, n/N (%)	7/209 (3%)	5/208 (2%)	0.57

B. Patients without obesity and patients with obesity class II and III

	Patients without obesity n = 212	**Patients with obesity class II and III n = 70**	**p**
Analgesia and delirium assessment			
At least one episode of severe pain, n (%)	80 (38%)	26 (37%)	0.93
At least one episode of moderate pain, n (%)	127 (60%)	47 (67%)	0.28
At least one episode of severe or moderate pain during nursing care, n (%)	104 (49%)	37 (53%)	0.58
At least one episode of delirium, n (%)	48 (23%)	20 (29%)	0.31
Complications, length of stay and mortality			
Revision surgery, n (%)	65 (31%)	23 (33%)	0.73
Sepsis, n (%)	69 (33%)	28 (40%)	0.25
Length of ICU stay	11 [8-16]	12 [8-22]	0.15
Mortality in ICU, n/N (%)	11/209 (5%)	0/68 (0%)	0.060
Mortality at day 28, n/N (%)	7/209 (3%)	0/68 (0%)	0.13

VIII. FIGURES

FIGURE 1. Flowchart of the study

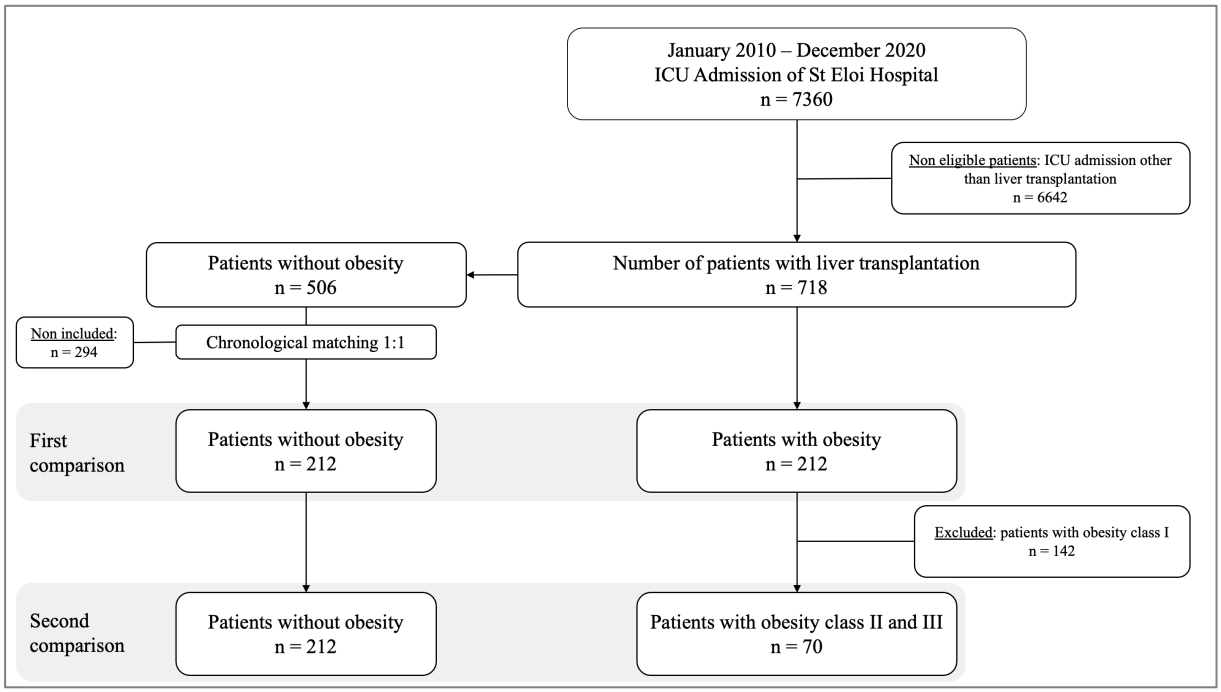
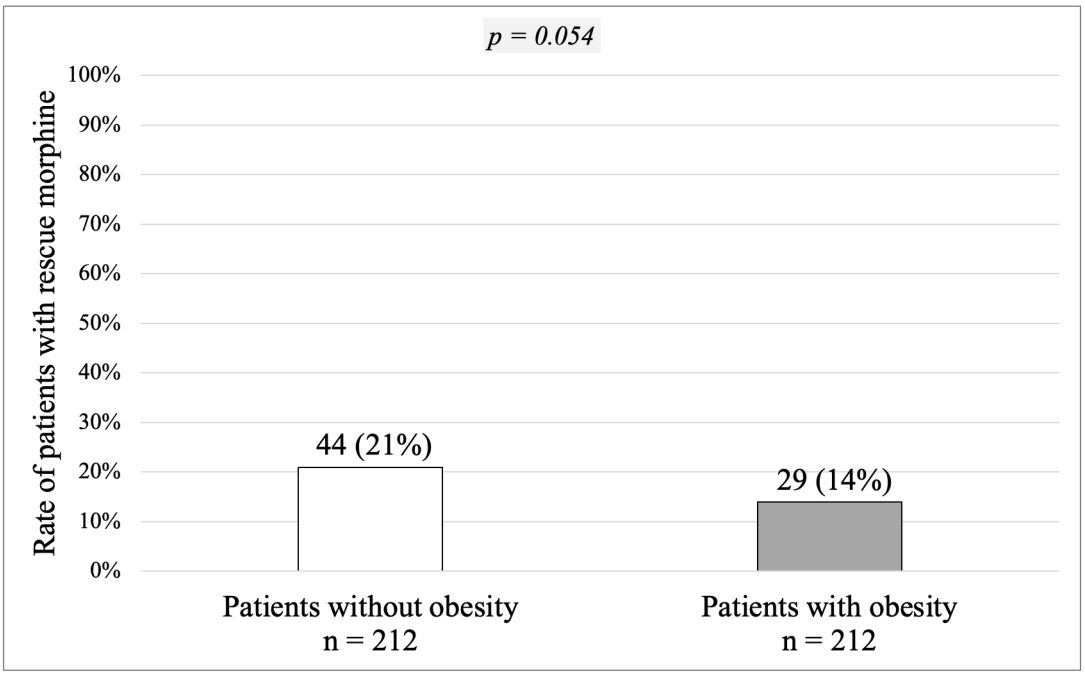


FIGURE 2. Primary endpoint: rate of rescue morphine analgesic consumption during the first 7 days of ICU stay.

Comparison of rate of rescue morphine analgesic consumption during the first 7 days of hospitalization in ICU between patients without obesity and patients with obesity (A), and comparison between patients without obesity and patients with obesity class II and III (B).

A. Patients without obesity and with obesity



B. Patients without obesity and with obesity class II and III

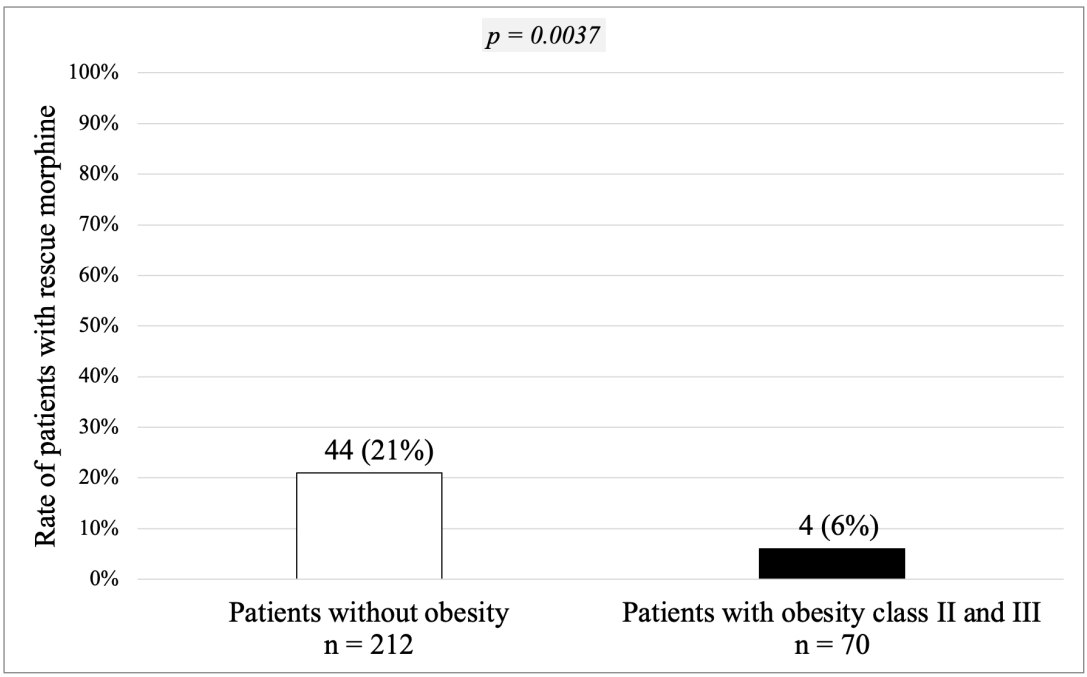
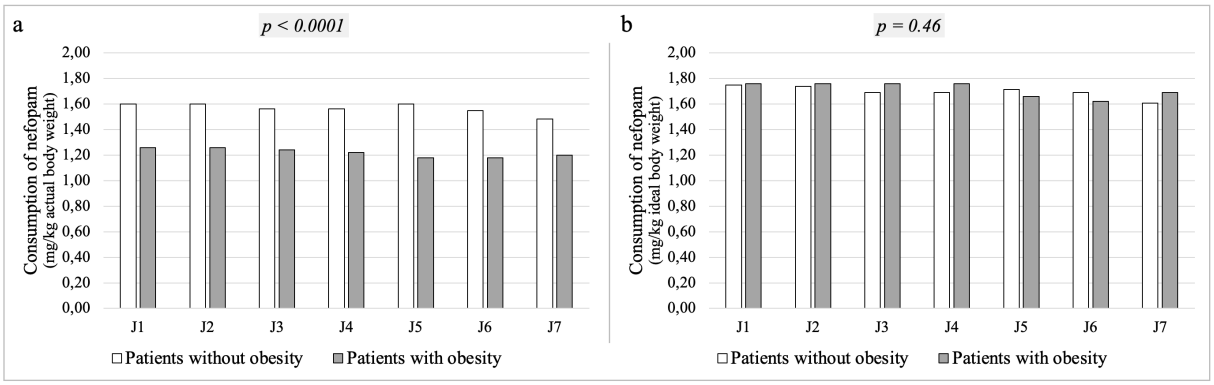


FIGURE 3. Secondary endpoints: overall consumption of nefopam during the first 7 days of ICU stay.

Comparison of overall consumption of nefopam during the first 7 days of ICU stay, in mg/kg of actual (a) and ideal (b) body weight, assessed daily until Day-7 between patients without obesity and patients with obesity (A), and comparison between patients without obesity and patients with obesity class II and III (B).

A. Patients without obesity and with obesity



B. Patients without obesity and with obesity class II and III

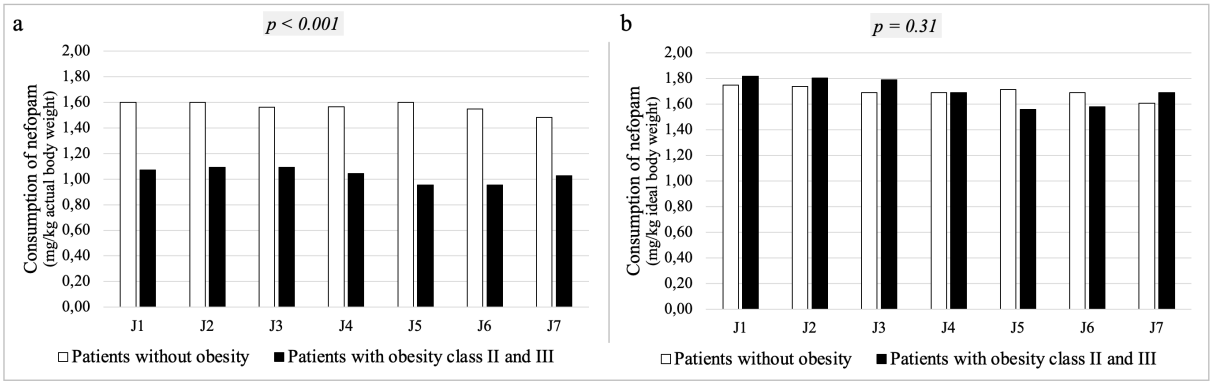
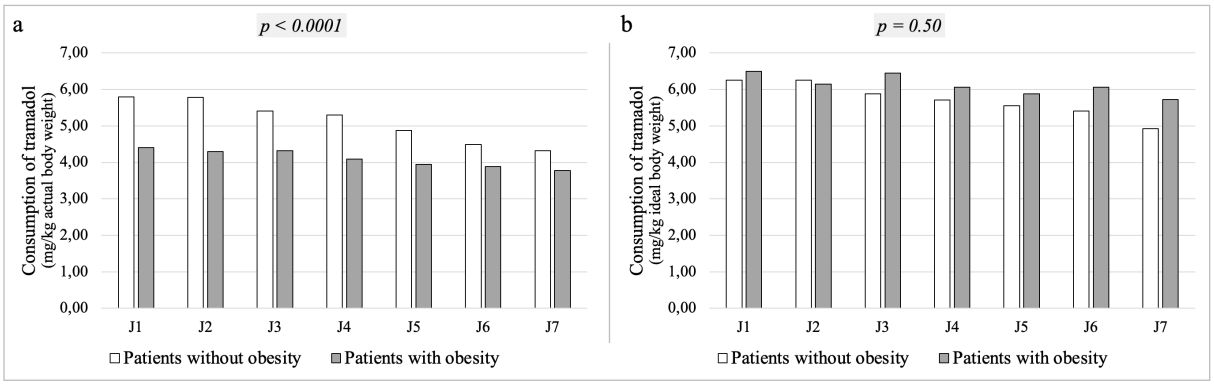


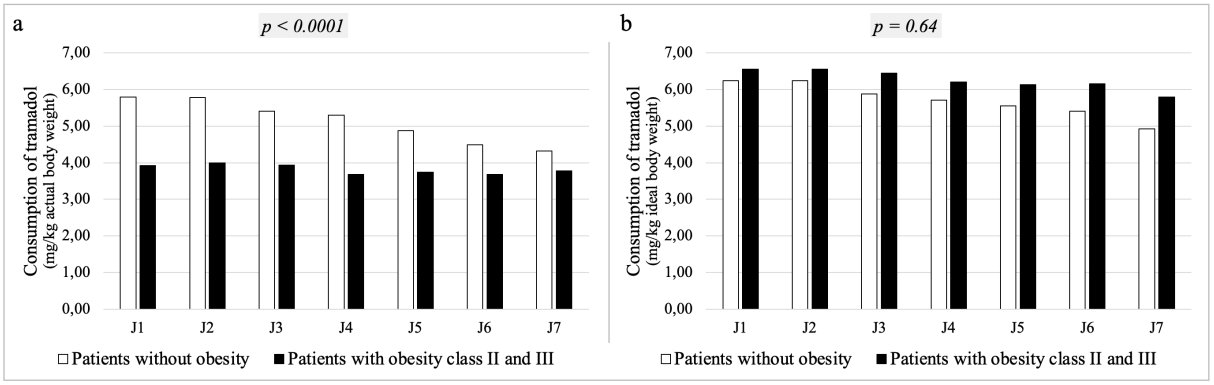
FIGURE 4. Secondary endpoints: overall consumption of tramadol during the first 7 days of ICU stay.

Comparison of overall consumption of tramadol during the first 7 days of ICU stay, in mg/kg of actual (a) and ideal (b) body weight, assessed daily until Day-7, with comparison between patients without obesity and patients with obesity (A), and comparison between patients without obesity and patients with obesity class II and III (B).

A. Patients without obesity and with obesity



B. Patients without obesity and with obesity class II and III



IX. APPENDIX

APENDIX 1. Secondary endpoints: RASS levels.

Comparison of RASS levels assessed daily until Day-7 between patients without obesity and patients with obesity (A), and between patients without obesity and patients with obesity class II and III (B). Continuous data are expressed in median [25th-75th percentiles].

A. Patients without obesity and patients with obesity

	Patients without obesity	**Patients with obesity**	**p**
RASS minimum			
J1	-1 [-4 ; 0]	-1 [-5; 0]	0.86
J2	-1 [-1 ; 0]	0 [-2; 0]	0.95
J3	0 [-1 ; 0]	0 [-1; 0]	0.62
J4	0 [-1 ; 0]	0 [-1; 0]	0.74
J5	0 [-1 ; 0]	0 [-1; 0]	0.073
J6	0 [-1 ; 0]	0 [-1; 0]	0.007
J7	0 [-1 ; 0]	0 [-1; 0]	0.59
RASS maximum			
J1	0 [0 ; 0]	0 [0; 0]	0.031
J2	0 [0 ; 0]	0 [0; 0]	0.70
J3	0 [0 ; 0]	0 [0; 0]	0.42
J4	0 [0 ; 0]	0 [0; 0]	0.35
J5	0 [0 ; 0]	0 [0; 0]	0.50
J6	0 [0 ; 0]	0 [0; 0]	0.19
J7	0 [0 ; 0]	0 [0; 0]	0.60

B. Patients without obesity and with obesity class II and III

	Patients without obesity	Patients with obesity class II and III	p
RASS minimum			
J1	-1 [-4 ; 0]	-1 [-5 ; 0]	0.90
J2	-1 [-1 ; 0]	-1 [-3 ; 0]	0.49
J3	0 [-1 ; 0]	0 [-1 ; 0]	0.34
J4	0 [-1 ; 0]	0 [-1 ; 0]	0.89
J5	0 [-1 ; 0]	0 [-1 ; 0]	0.18
J6	0 [-1 ; 0]	0 [-1 ; 0]	0.048
J7	0 [-1 ; 0]	0 [-1 ; 0]	0.42
RASS maximum			
J1	0 [0 ; 0]	0 [-1 ; 0]	0.007
J2	0 [0 ; 0]	0 [0 ; 0]	0.31
J3	0 [0 ; 0]	0 [0 ; 0]	0.13
J4	0 [0 ; 0]	0 [0 ; 0]	0.28
J5	0 [0 ; 0]	0 [0 ; 0]	0.10
J6	0 [0 ; 0]	0 [0 ; 0]	0.014
J7	0 [0 ; 0]	0 [0 ; 0]	0.18

APPENDIX 2. Secondary endpoints: number of surgical drains and type (tubular, salem, biliary, other).

Comparison of number of surgical drains assessed daily until Day-7 between patients without obesity and patients with obesity (A), and between patients without obesity and patients with obesity class II and III (B). Continuous data are expressed in median [25th-75th percentiles].

A. Patients without obesity and with obesity

	Patients without obesity	**Patients with obesity**	**p**
Tubular drains			
J1	2 [1-2]	1 [1-2]	0.19
J2	2 [1-2]	1 [1-2]	0.16
J3	2 [1-2]	1 [1-2]	0.17
J4	2 [1-2]	1 [1-2]	0.26
J5	2 [1-2]	1 [1-2]	0.009
J6	2 [1-2]	1 [1-2]	0.039
J7	2 [1-2]	1 [1-2]	0.47
Salem probe			
J1	1 [1-1]	1 [1-1]	0.51
J2	1 [1-1]	1 [1-1]	0.23
J3	1 [1-1]	1 [1-1]	0.24
J4	1 [1-1]	1 [1-1]	0.55
J5	1 [1-1]	1 [1-1]	0.31
J6	1 [1-1]	1 [1-1]	0.88
J7	1 [1-1]	1 [1-1]	0.94
Biliary drains			
J1	1 [1-1]	1 [1-1]	0.51
J2	1 [1-1]	1 [1-1]	0.23
J3	1 [1-1]	1 [1-1]	0.24
J4	1 [1-1]	1 [1-1]	0.55
J5	1 [1-1]	1 [1-1]	0.31
J6	1 [1-1]	1 [1-1]	0.88
J7	1 [1-1]	1 [1-1]	0.94
Other types of drains			
J1	1 [1-2]	1 [1-2]	0.74
J2	1 [1-2]	1 [1-3]	0.74
J3	1 [1-2]	1 [1-3]	0.54
J4	1 [1-2]	2 [1-3]	0.23
J5	1 [1-2]	2 [1-2]	0.50
J6	1 [1-2]	1 [1-2]	0.72
J7	1 [1-2]	1 [1-3]	0.40

Total number of drains			
J1	4 [3-5]	4 [3-5]	<0.001
J2	4 [3-5]	3 [3-4]	0.006
J3	4 [3-4]	3 [2-4]	0.040
J4	3 [2-4]	3 [2-4]	0.20
J5	3 [2-4]	3 [2-4]	0.019
J6	3 [2-4]	3 [2-4]	0.11
J7	3 [2-4]	3 [2-4]	0.35

B. Patients without obesity and with obesity class II and III

	Patients without obesity	**Patients with obesity class II and III**	**p**
Tubular drains			
J1	2 [1-2]	1 [1-2]	0.088
J2	2 [1-2]	1 [1-2]	0.13
J3	2 [1-2]	1 [1-2]	0.12
J4	2 [1-2]	1 [1-2]	0.22
J5	2 [1-2]	1 [1-2]	0.017
J6	2 [1-2]	1 [1-2]	0.078
J7	2 [1-2]	1 [1-2]	0.38
Salem probe			
J1	1 [1-1]	1 [1-1]	0.89
J2	1 [1-1]	1 [1-1]	0.27
J3	1 [1-1]	1 [1-1]	0.36
J4	1 [1-1]	1 [1-1]	0.35
J5	1 [1-1]	1 [1-1]	0.20
J6	1 [1-1]	1 [1-1]	0.80
J7	1 [1-1]	1 [1-1]	0.80
Biliary drains			
J1	1 [1-1]	1 [1-1]	0.89
J2	1 [1-1]	1 [1-1]	0.27
J3	1 [1-1]	1 [1-1]	0.36
J4	1 [1-1]	1 [1-1]	0.35
J5	1 [1-1]	1 [1-1]	0.20
J6	1 [1-1]	1 [1-1]	0.80
J7	1 [1-1]	1 [1-1]	0.80
Other types of drains			
J1	1 [1-2]	1 [1-3]	0.88
J2	1 [1-2]	1 [1-3]	0.81
J3	1 [1-2]	2 [1-3]	0.40
J4	1 [1-2]	2 [1-3]	0.18
J5	1 [1-2]	1 [1-2]	0.92
J6	1 [1-2]	1 [1-2]	0.99
J7	1 [1-2]	1 [1-3]	0.72

Total number of drains			
J1	4 [3-5]	4 [3-4]	<0.001
J2	4 [3-5]	4 [2-4]	0.038
J3	4 [3-4]	3 [2-4]	0.058
J4	3 [2-4]	3 [2-4]	0.31
J5	3 [2-4]	3 [2-4]	0.011
J6	3 [2-4]	3 [2-4]	0.11
J7	3 [2-4]	3 [2-4]	0.22

APPENDIX 3. Secondary endpoints: liver biomarkers of graft recovery and serum albumin levels.

Comparison of liver biomarkers of graft recovery: prothrombin (%), factor V (%), bilirubin total and conjugated (µmol/L), aspartate transaminase (UI/L), alanine transaminase (UI/L) and serum albumin levels (g/L) assessed daily until Day-7 between patients without obesity and patients with obesity (A), and between patients without obesity and patients with obesity class II and III (B). Continuous data are expressed in median [25th-75th percentiles].

A. Patients without obesity and with obesity

	Patients without obesity	**Patients with obesity**	**p**
Prothrombin			
Admission in ICU	50 [41-61]	47 [38-55]	0.016
J1	56 [45-66]	53 [43-64]	0.088
J2	70 [56-81]	69 [55-80]	0.34
J3	77 [65-90]	76 [65-90]	0.78
J4	80 [68-92]	81 [69-91]	0.97
J5	82 [69-94]	82 [70-91]	0.98
J6	81 [72-91]	83 [72-91]	0.94
J7	83 [70-94]	83 [72-94]	0.58
Factor V			
Admission in ICU	37 [28-47]	33 [25-43]	0.019
J1	56 [39-72]	55 [39-74]	0.74
J2	75 [52-102]	81 [61-101]	0.35
J3	91 [66-116]	95 [76-115]	0.25
J4	98 [77-126]	109 [87-128]	0.055
J5	112 [89-139]	107 [88-136]	0.75
J6	120 [93-145]	122 [95-148]	0.47
J7	121 [97-147]	120 [98-150]	0.44
Total bilirubin			
Admission in ICU	106 [63-186]	105 [66-177]	0.94
J1	102 [55-168]	99 [59-181]	0.83
J2	77 [34-133]	71 [40-141]	0.67
J3	77 [36-130]	67 [36-131]	0.83
J4	74 [35-132]	67 [37-133]	0.93
J5	76 [33-143]	78 [35-140]	0.84
J6	73 [34-135]	79 [37-160]	0.37
J7	67 [33-142]	71 [35-163]	0.55
Conjugated bilirubin			
Admission in ICU	69 [38-124]	68 [39-119]	0.86
J1	73 [35-113]	65 [38-132]	0.86

J2	57 [23-96]	53 [26-105]	0.81
J3	55 [24-103]	50 [25-100]	0.91
J4	58 [23-105]	53 [24-105]	0.97
J5	56 [22-110]	60 [25-117]	0.72
J6	56 [21-108]	63 [24-131]	0.28
J7	56 [21-112]	54 [23-132]	0.58
Aspartate transaminase			
Admission in ICU	661 [373-1278]	681 [372-1262]	0.99
J1	465 [296-1059]	523 [283-1022]	0.53
J2	267 [149-573]	291 [161-531]	0.46
J3	163 [99-278]	170 [101-293]	0.39
J4	88 [56-167]	101 [70-163]	0.060
J5	62 [38-104]	71 [49-117]	0.020
J6	53 [33-79]	59 [39-93]	0.045
J7	45 [30-81]	51 [35-76]	0.26
Alanine transaminase			
Admission in ICU	448 [232-817]	449 [236-845]	0.91
J1	415 [245-791]	452 [228-816]	0.90
J2	349 [189-669]	361 [180-684]	0.86
J3	296 [156-526]	288 [150-521]	0.98
J4	223 [123-394]	240 [132-413]	0.41
J5	165 [98-297]	203 [115-319]	0.082
J6	139 [84-256]	170 [91-279]	0.11
J7	124 [72-220]	143 [87-221]	0.26
Serum albumin level			
Admission in ICU	29 [26-31]	29 [26-32]	0.81
J1	31 [29-35]	31 [29-34]	0.22
J2	33 [31-36]	33 [30-36]	0.15
J3	34 [31-38]	34 [31-37]	0.74
J4	34 [30-37]	33 [31-36]	0.94
J5	33 [30-35]	32 [30-35]	0.24
J6	32 [29-35]	31 [28-34]	0.046
J7	31 [29-34]	31 [28-33]	0.20

B. Patients without obesity and with obesity class II and III

	Patients without obesity	Patients with obesity class II and III	p
Prothrombin			
Admission in ICU	50 [41-61]	48 [39-55]	0.069
J1	56 [45-66]	50 [43-59]	0.028
J2	70 [56-81]	67 [53-80]	0.33
J3	77 [65-90]	76 [63-91]	0.73
J4	80 [68-92]	79 [66-91]	0.52
J5	82 [69-94]	82 [69-92]	0.75
J6	81 [72-91]	81 [72-91]	0.91
J7	83 [70-94]	84 [71-97]	0.48
Factor V			
Admission in ICU	37 [28-47]	34 [25-43]	0.13
J1	56 [39-72]	52 [38-68]	0.48
J2	75 [52-102]	79 [51-98]	0.84
J3	91 [66-116]	91 [67-117]	0.83
J4	98 [77-126]	112 [79-135]	0.30
J5	112 [89-139]	104 [86-141]	0.79
J6	120 [93-145]	122 [95-148]	0.66
J7	121 [97-147]	121 [100-150]	0.37
Total bilirubin			
Admission in ICU	106 [63-186]	107 [71-162]	0.86
J1	102 [55-168]	116 [53-203]	0.69
J2	77 [34-133]	86 [42-149]	0.25
J3	77 [36-130]	77 [38-145]	0.51
J4	74 [35-132]	83 [40-152]	0.31
J5	76 [33-143]	87 [43-157]	0.26
J6	73 [34-135]	92 [42-161]	0.18
J7	67 [33-142]	89 [45-156]	0.22
Conjugated bilirubin			
Admission in ICU	69 [38-124]	69 [41-101]	0.98
J1	73 [35-113]	70 [36-142]	0.59
J2	57 [23-96]	60 [29-107]	0.36
J3	55 [24-103]	64 [29-105]	0.45
J4	58 [23-105]	64 [28-119]	0.30
J5	56 [22-110]	66 [27-126]	0.24
J6	56 [21-108]	74 [31-130]	0.12
J7	56 [21-112]	69 [32-117]	0.26
Aspartate transaminase			
Admission in ICU	661 [373-1278]	751 [332-1296]	0.85
J1	465 [296-1059]	566 [288-1253]	0.40
J2	267 [149-573]	327 [172-597]	0.36
J3	163 [99-278]	168 [101-354]	0.45

J4	88 [56-167]	99 [68-166]	0.27
J5	62 [38-104]	72 [51-106]	0.077
J6	53 [33-79]	58 [37-88]	0.19
J7	45 [30-81]	51 [36-80]	0.28
Alanine transaminase			
Admission in ICU	448 [232-817]	479 [209-845]	0.84
J1	415 [245-791]	567 [240-835]	0.40
J2	349 [189-669]	387 [186-684]	0.72
J3	296 [156-526]	302 [145-555]	0.89
J4	223 [123-394]	227 [124-393]	0.81
J5	165 [98-297]	189 [118-324]	0.30
J6	139 [84-256]	168 [91-291]	0.27
J7	124 [72-220]	148 [87-221]	0.36
Serum albumin level			
Admission in ICU	29 [26-31]	29 [26-31]	0.53
J1	31 [29-35]	30 [28-33]	0.13
J2	33 [31-36]	32 [31-35]	0.17
J3	34 [31-38]	34 [31-37]	0.65
J4	34 [30-37]	33 [31-36]	0.91
J5	33 [30-35]	32 [30-35]	0.66
J6	32 [29-35]	31 [29-34]	0.27
J7	31 [29-34]	30 [28-33]	0.044

SERMENT

- *En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Etre suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.*

- *Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.*

- *Admis (e) dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*

- *Respectueux (se) et reconnaissant (e) envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*

- *Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert (e) d'opprobre et méprisé (e) de mes confrères si j'y manque.*

<u>OB-Pain</u> : Douleur au décours d'une transplantation hépatique chez les patients atteints d'obésité par rapport aux patients non atteints d'obésité

Objectif : Comparer le recours à la morphine dans les suites post-opératoires d'une transplantation hépatique chez les patients atteints ou non d'obésité.

Méthode : Nous avons réalisé une analyse rétrospective de données prospectivement incluses via un logiciel informatique de janvier 2010 à décembre 2020 incluant l'ensemble des patients ayant eu une transplantation hépatique et atteints d'obésité. Un groupe contrôle, composé de patients non atteints d'obésité (Indice de Masse Corporelle IMC < 30 kg/m²), a été défini selon un appariement chronologique en 1:1. L'étude comportait deux niveaux de comparaisons : le premier comparait les patients non atteints d'obésité avec les patients atteints d'obésité, la seconde comparait les patients non atteints d'obésité avec les patients atteints d'obésité classes II et III. Le critère de jugement principal était le taux de patients ayant recours aux morphiniques au cours des 7 premiers jours en réanimation. Les critères de jugement secondaires étaient la survenue au cours des 7 premiers jours en réanimation d'au moins un épisode douloureux sévère, modéré ou au cours d'un soin, d'un épisode confusionnel, ainsi que la consommation quotidienne en néfopam et tramadol, l'évaluation quotidienne de la vigilance par le RASS (Richmond Agitation Sedation Scale), le nombre de drains chirurgicaux, les marqueurs biologiques de récupération hépatique, puis les complication survenues (sepsis et reprise chirurgicale), la durée de séjour en réanimation et la mortalité en réanimation et à J28.

Résultats : Deux-cent douze patients non atteints d'obésité (dont 70 patients avec obésité sévère) ont été appariés avec 212 patients atteints d'obésité. Parmi les patients non atteints d'obésité, 44 (21%) ont eu recours aux morphiniques. En comparaison, chez les patients atteints d'obésité, 29 (14%) ont eu recours aux morphiniques (p = 0,054) ; et chez les patients atteints d'obésité classes II et III, 4 (6%) ont eu recours aux morphiniques (p = 0,0037). Aucune différence significative n'a été observée concernant les critères de jugement secondaires.

Conclusion : Les patients atteints d'obésité sévère ont moins recours aux morphiniques après une transplantation hépatique que les patients non atteints d'obésité, pour des niveaux de douleur comparables sous protocole d'analgésie comparable (néfopam et tramadol en posologie adaptée au poids idéal théorique).

Mots clés : DOULEUR, ANALGESIE, OBESITE, TRANSPLANTATION HEPATIQUE, REANIMATION