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The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery : a randomized, multicentre, double blind, study

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Key words: surgery; glucocorticoid; dexamethasone; post-operative complications; pneumonia

ABSTRACT

Introduction Postoperative complications are major healthcare problems and are associated with a reduced short-term and long-term survival after surgery. An excessive postoperative inflammatory response participates to the development of postoperative infection and mortality. The aim of the PACMAN study is to assess the effectiveness of perioperative administration of corticosteroid to reduce postoperative morbidity and mortality in patients undergoing major non-cardiac surgery.

Methods and analysis: The PACMAN is a multicentre, randomized, controlled, double blind, two-arms trial of 1222 high-risk patients aged 50 years of older undergoing major non-cardiac surgery at 32 acute care hospital in France. Patients are randomly assigned to dexamethasone (0,2mg.kg-1 at the end of the surgical procedure, and at day+1, n=611) or to placebo (n=611). The primary outcome is a composite of predefined 14-day moderate or major pulmonary complications and mortality. Secondary outcomes are surgical complications, infections, organ failures, critical care–free days, length of hospital stay and all-cause mortality at 28 days.

Ethics and dissemination: The PACMAN trial protocol has been approved by the ethics committee of Sud Mediterranée V, and will be carried out according to the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The PACMAN trial is the first randomized controlled trial powered to investigate whether perioperative administration of corticosteroids in patients undergoing non-cardiac major surgery reduce postoperative complications. The results of this study will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

Trial registration number clinicaltrials.gov NCT03218553

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is a multicenter, randomized, controlled and double blind trial adequately powered to determine whether corticosteroid reduces postoperative complications in high risk patients undergoing major non-cardiac surgery.
- Treatment's benefits include reduced risk of postoperative infection, development of organ failure and reduced risk of mortality.
- Limitations due to the difficulty of sepsis diagnosis after major surgery are limited by the use of a placebo ensuring a double-blind evaluation of the primary outcome.
- This large study has the potential of changing international recommendations on the management of high risk patients undergoing major non-cardiac surgery.

INTRODUCTION

More than 300 million major surgical procedures are undertaken worldwide each year [1]. For most patients, risks of surgery are low. However in an European international cohort, the mortality rate for patients undergoing non-cardiac surgery was higher than excepted (4% of patients died before hospital discharge) [2]. It is interesting to consider that 10% of patients at risk of postoperative complications represent 80% of postoperative deaths [3]. It is also important to consider that patients who develop complications but survive until hospital discharge have usually reduced functional independence and long-term survival [4]. These data suggest that interventions to prevent complications and mortality should probably be undertaken early. One of the main targets to focus on is probably lung. Indeed, postoperative respiratory complications represent the most common perioperative complication after wound infections with an estimated incidence ranging from 2.0% to 5.6% for surgical procedures [4]. Respiratory failure after general anaesthesia and tracheal extubation has been shown to be one of the most meaningful factors associated with poor patient outcomes, leading to longer hospital stay [4]. Considering, the high volume of surgical procedures undertaken each year, the key message is that decreasing even a low rate of avoidable harm will be associated with a high cost saving for the society and many preventable deaths and complications for the patients.

Major surgery induces an inflammatory response characterized by activation of platelets, neutrophils, monocytes, macrophages, cascades (coagulation, fibrinolytic, and kallikrein). The consequences of tissue surgical injuries are a release of danger-associated molecular patterns which initiate the production of pro-inflammatory mediators (cytokines, radical oxygen species) [5]. This inflammatory response is useful for tissue healing, but it is thought that an excessive response contributes to post-operative morbidity (such as infections and organ failures) and mortality. Glucocorticoids have thus been proposed to reduce the risk of complications in several medical conditions characterized by systemic inflammatory response.

In patients undergoing major cardiac surgery, corticosteroids reduce the risk of atrial fibrillation and the duration of mechanical ventilation [17]. In severe trauma patients, considering the potential immunostimulating effects of “low doses” corticosteroids [6], we have shown, in two multicentre, randomized, double blind placebo-controlled study on intubated trauma patients, that the use of an intravenous low-dose corticosteroids, compared with placebo, resulted in a decreased risk of hospital- acquired pneumonia [7,8]. Interestingly, apart from higher insulin consumption in patients receiving corticosteroids, no significant harm related to treatment was recorded in both studies.

Finally, the use of corticotherapy to enhance recovery after major non cardiac surgery is not recommended. The objective of the PACMAN study is to ascertain whether or not the administration of early corticosteroid with standard care compared with standard care alone

prevents respiratory complications and reduces mortality in high-risk patients undergoing major surgery. We are reporting the version 4 of the protocol (2nd September 2017). This manuscript has been submitted for publication on the 30th of November 2017, before the inclusion of the first patient in the study.

Methods and Design

Hypothesis

High-risk patients treated with short course of corticosteroid have reduced morbidity and mortality rates compared to those receiving standard care alone after major non-cardiac surgery.

Research Questions

1. Does short-course of moderate doses of dexamethasone prevent death and/or post-operative respiratory complications after major non-cardiac surgery in high-risk patients ?
2. Does short-course of moderate doses of dexamethasone reduce the duration of hospitalization after major non-cardiac surgery in high-risk patients ?
3. Does short-course of moderate doses of dexamethasone prevent delayed skin healing ?

Design

The Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac surgery (PACMAN) study is a multicenter, randomized, double blind, parallel-group, controlled trial (Figure 1).

Ethic

The Institutional Review Board of Sud Mediterranée V (France) approved the study protocol (June 2017). Patients provide written consent for participation. The PACMAN trial is conducted in accordance with the declaration of Helsinki and is registered on June 2017 at http://clinicaltrial.gov/ with trial registration NCT03218553.

Setting

The study involved 33 French hospitals, each centre caring for more than 200 patients undergoing major surgery each year.

Study population

Investigators screen consecutive high-risk patients undergoing major non-cardiac surgery. Patients older than 50 years and scheduled for a major surgery (> 90 minutes and performed under general anesthesia) of the abdomen, pelvis, thorax, face/neck, vascular surgery are eligible provided that they have one or more of the following risk factors : age > 65 years, presence of a defined risk factor for cardiac or respiratory disease (exercise tolerance equivalent to 6 metabolic equivalents or less), medical history of stroke, moderate to severe renal impairment (clearance of creatinine ≤ 30 mll/L), active smoking, averaged observed blood losses over 500 ml or emergency surgery. These risk factors have been adapted from the systematic review for the preoperative pulmonary risk

stratification for non-cardiothoracic surgery published by the American College of Physicians [9] and from the guidelines for the management of severe perioperative bleeding of the European Society of Anesthesiology [10]. Exclusions criteria are: allergy to the intravenous formulation of dexamethasone, treatment with systemic corticosteroids at a dose > 5 mg.day-1 of equivalent prednisolone in the previous 3 months, uncontrolled psychotic disorder (acute or chronical) chronic renal failure (clearance of creatinine < 10 ml/min), life expectancy of less than 1 month, preoperative shock (defined by the need for continuous infusion of vasoactive drugs (norepinephrine, epinephrine or dobutamine), acute pulmonary edema in the last 7 days, active bacterial or viral infection, pregnant women, breastfeeding women, minors, Adults under guardianship or trusteeship.

Treatment Allocation

Patients are randomized in a 1:1 ratio and stratified according to cancer (yes/no) and according to the type of surgical procedure (thoracic surgery or not). Randomisation is made by a computerized number generator list provided by a statistician not involved in the determination of eligibility or in the assessment of outcomes. All assignments are made through a dedicated, pass-word protected, SSL-encrypted website. Patients are randomized in the first 24 prior to surgery to dexamethasone (intervention group) or to placebo (control group).

Masking protocol

Randomized patients are given a number corresponding to a «PACMAN treatment pack» that contains: 4 x 10 mg vial of dexamethasone or placebo, and a sheet for schedule administration.

Procedures

At the end of the surgery (< 2 hours after skin closure), and before study drug administration, the blood level of c-reactive protein (CRP) is measured (Figure 1). Then, patients randomized to either intravenous infusion of dexamethasone (0.2 $mg.kg^{-1}$ of real body-weight immediately within the 2 hours after the end of the surgery, and at day+1) or injection of placebo receive treatment (Figure 1). The blood level of CRP is measured at day+1 and day+2 after surgery. The treatment is administrated independently of the CRP levels.

Standard of care

According to recent recommendations and publications, clinicians are prompted to realise adequate timing of antimicrobial prophylaxis [11], to apply a protective ventilation strategy (low tidal volume and Positive End Expiratory Pressure) during surgery [12], to closely monitor and treat peroperative hypovolemia and hypotension [13,14] and to early stop sedation at the end of the

surgery [15]. Decisions of post-operative admission to intensive care unit and of prophylactic application of non-invasive ventilation will follow local standard of cares.

Protocol drop-out

For patients developing an allergic reaction to the study treatment, the second injection will not be performed and the appropriate treatment of the allergic reaction will be provided. Patients with allergic reaction to dexamethasone will be kept in analysis and remain analysis with the intervention group. Clinicians can use glucocorticoid during the first 7 days of the study only in case of formal indication of steroid (rescue treatment). Patients treated with out-of-protocol glucocorticoid will be kept in analysis and remain analysis with their attributed group.

Study end points

The primary outcome is a composite outcome (all-cause mortality and major postoperative complications) within 14 days after surgery, at least one item among the following: postoperative sepsis, Postoperative pulmonary complication (postoperative pneumonia, need for invasive ventilation and/or noninvasive ventilation for respiratory failure) and all-cause mortality.

Secondary outcomes are all-cause mortality at 28 days, duration of invasive mechanical ventilation, duration of non-invasive mechanical ventilation, hospital free-days at 28 days, surgical complications according to the Clavien-Dindo classification within 28 days, unplanned admission or readmission to intensive care units (within 28 days following randomization), organ failures within 14 days after surgery, Sequential Organ Failure Assessment (SOFA) at day+1 and day+3, proportion of patients who experienced adverse events, especially hyperglycaemia, healing impairment at day +14 after surgery.

Follow-up Data

The following variables are collected: demographics, American Society of Anesthesiology (ASA) score, pre-operative medical optimization, per-surgery management (drugs, mechanical ventilation, durations of procedure, fluid infusion, bleeding, post-operative analgesia), infections, organ failures, blood levels of CRP, healing, post-operative complications, length of ventilator support, and ICU hospitalisation and death at day 28 are recorded.

Data Collection and Checking

Data will be entered into the electronic web-based (Clinsight) case report form (eCRF) by trial or clinical personnel under the supervision of the study site investigators. From the eCRFs the trial database will be established.

Study Monitoring

The study will be monitored on behalf of the promotor (Nantes University Hospital). Site staff will be available to facilitate the monitoring visits and ensure that all required documentation is

available for review. Study initiation visits are carried out at all sites before recruitment starts at that site. During regular monitoring visits realized throughout the duration of the trial, an independent research assistant will carry out Source Data Verification of trial data, verify informed consent forms and ensure the completeness of the Investigator Site Files.

Study Oversight

Study sponsor is the Nantes University Hospital (5 allée de l'ile Gloriette, 44000 Nantes, drc-nantes@chu-nantes.fr). Experienced research staff will monitor the study for quality, the integrity of data in all the participating centers. Serious adverse events and unexpected related or possibly related serious events are reported blinded to the promotor within respectively 24 hours or 7 days. An independent data and safety monitoring board (DSMB) is appointed by the sponsor. The DSMB is made up of 4 individuals with no connection to the research, including three clinician specializing in the management of ICU patients and corticotherapy in ICU, and a methodologist/biostatistician. Before the first inclusion, and every 300 inclusions, the DSMB looks over the ethics in accordance with the Declaration of Helsinki, monitors patient safety and reviews safety issues as the study progresses. The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the research in light of serious adverse reactions.

The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the research. Trial recruitment can be stopped by the promotor on the advice of the DSMB in case of safety concern.

Roles of the sponsor and of the funder

The sponsor and the funder have no role in the design or conduct of the study, the data analysis, the writing of the manuscript or in the decision to submit the manuscript.

Statistical consideration

All analyses will be performed with the use of SAS software (version 9.4, NC, USA) before the breaking of the randomization code, according to International Conference on Harmonization-Good Clinical Practice guidelines. Analyzes will be conducted, first, on data from the modified intention-to-treat (modified-ITT) population, second, in the intention-to-treat (ITT) population as well as in the per-protocol population. The criteria for including patients in the modified-ITT and in the per-protocol populations, respectively, are provided below.

Continuous variables will be presented as mean and standard deviations (as median and quartiles, otherwise) and will be compared with the use of the unpaired *t* test or the Mann-Whitney *U* test when appropriate. The Shapiro-Wilk test will be used to assess normality, and the Fisher-Snedecor test to assess homoscedasticity. Categorical data will be presented as exact numbers and percentages.

Number of patients

The rate of the primary endpoint in the control group is expected to reach 20% [12,16]. Assuming a 20% rate in the control group and 14% in the dexamethasone group, A total of 1222 patients are needed to detect this difference between the two groups with a 5% type I error and a power of 80% in a two-sided test.

Pre-Planned primary analysis

For the primary analysis, data will be analysed with the use of logistic regression adjusted for stratification factors (cancer and thoracic procedure).

The effects of the treatment will be investigated in ITT, in modified-ITT and in per-protocol populations. **In the ITT analyse,** all randomized patients will be kept in analysis. In the **modified-ITT analyse,** all randomized patients will be kept in analysis except those who would not have been eligible for randomization according to the inclusion/non-inclusion criteria or those who have not received any injection of the experimental treatment (dexamethasone or placebo). In the **per-protocol analyse,** all randomized patients will be kept in analysis except patients having one or more major protocol violations defined as those who would not be eligible for randomization according to inclusion/non-inclusion criteria; or those who accidentally would have received the wrong intervention (Dexamethasone or placebo); or those in whom surgical intervention could not have been done (for example, intra-abdominal extensive cancer); or those who have withdrawn consent; those who would have received out-of-protocol glucocorticoids.

Planned sub-group analyses:

- Strates of randomization (cancer yes/no, thoracic procedure yes/no)
- According to the level of CRP measured at the end of the surgical procedure immediately before the first injection of the studied treatment (< 50, 50-150 or > 150 mg/mL).
- In diabetic and non-diabetic patients.

No interim efficacy analyze will be performed so that no adjustment is required to the final p-value to allow for the multiple testing. The DSMB will only analyse safety data and can make recommendation for adjustment of the number of patients to be included to ensure the statistical power of the mITT analysis.

Method for missing data

There should not be missing data for the primary outcome measure and the missing data rate

should be low for the other outcomes as well. Missing data will be described by treatment arm. According to the rate of missing data (over 5%) sensitivity analyses will be performed using multiple imputation methods as well as worst case scenario (missing data considered as the most unfavourable case) and maximum bias scenario (missing data considered as the most favourable or unfavourable case in the placebo and experimental arms respectively).

Data Sharing statement

The principle investigator will have access to the final trial data set. Data sharing: patient level data and/or full dataset and/or statistical code will be available upon request to the corresponding author. Consent for the data sharing was not obtained but the presented data are anonymised and risk of identification is low and the potential benefits of sharing these data outweigh the potential harms.

DISCUSSION

The PACMAN trial is the first randomized controlled study powered to investigate short-course of moderate dose of dexamethasone in patients undergoing major non-cardiac surgery.

Several trials have investigated the benefits of administering corticosteroids in patients undergoing major surgery. However, there is yet no agreement on the beneficial effects of corticosteroids in alleviating surgical stress. This disagreement probably stems from the variability in the drugs used, their dosage and administration schedule, and the surgical procedures in different studies. Also the fear of side effects induced by a possible immunosuppression (infections, postoperative wound complications, anastomotic leakage) explains the extreme variability of behaviour from one centre to another and among patients and physicians. These considerations prevented the performance of a large scale randomized study despite evidences that corticosteroids could enhance outcome and even decrease the rate of infections after non-cardiac major surgery (see above). Before general recommendations for perioperative corticosteroids administration can be made, obviously conclusive safety studies must be available. So far, there seem to be no safety issues [17-19] related to a single preoperative dose of corticosteroids including specific studies on wound healing [20,21]. The consequences of perioperative use of corticosteroids for glucose homeostasis need further evaluation, but so far the transitory increased hyperglycemic response has not been related to increased postoperative complications [22].

We will include patients considered as high risk of post-operative respiratory complications according to American and European recommendations [9] [10]. Risk factors of pulmonary complications are either related to the surgery, or to the medical history of the patients. We decided to not limit the PACMAN study to a specific type of surgery but to include all sort of surgery

provided that the expected duration of the procedure exceeds 90 minutes. This strategy maximises recruitment rates and improves the generalisation of results. We acknowledge that the clinical risk factors of postoperative respiratory complications are inconstantly used in clinical practice, which can limit the applicability to the study results. However, preoperative optimization by nutritional support , respiratory physiotherapy or smoking cessation are recommended in patients presenting such risk factors [9]. The selection of high risk patients will result in a high incidence rate of the primary endpoint, which will result in a study of high clinical relevance and statistical power.

We selected a composite outcome as the primary criteria. The use of mortality as a primary endpoint is never used in perioperative studies because the risk of death is low and the statistical power would be low. Respiratory complications are particularly frequent and serious after major surgery and we have recently proposed that glucocorticoid prevent the development of inflammation-related immunosuppression [6], and decrease the risk of pneumonia after severe trauma [7,8]. Finally, mortality is not competitive with the primary criteria since the outcome all cause of death is included in the composite primary outcome.

For the primary statistical analysis of the primary outcome, we will use a modified intention to treat analysis including patients fulfilling all the inclusion criteria and who have received at least one injection of the experimental treatment. This strategy has recently been used in randomized clinical trials evaluating peri-procedure treatments [14,23], because the time between the randomization, which is realized before the procedure, and the administration of the study treatment, which is realized during or after the procedure, expose the study to a high risk of included patients not receiving the allocated treatment (e.g. cancelled or delayed surgery or perioperative complications). In this setting, we strongly believe that the mITT is more accurate to the medical field than the ITT. However, the exclusion of patients in the mITT analysis can theoretically decrease the statistical power of the study. Thus, the DSMB will have access to the number of patients excluded from the miTT analysis, and if necessary the DMSB will have the responsibility to propose an increase of the number of patients to be included to guarantee the study power. Finally, the intention-to-treat analysis will be reported in the final version of the manuscript.

Trial status

The trial has already achieved many milestones. The trial is sponsored by the French ministry of health (PHRCN 2016_0442). Insurance for non-negligent harm has been provided by University Hospital of Nantes (France). Research ethics committee approval was obtained in September 2019 (Comité de Protection des Personnes Sud Méditerranée V). The French Agency for the safety of medicines and medical devices authorized the study in September 2017 (#170245RS-21). The study is registered with the American registry of trials (https://clinicaltrials.gov/ NCT03218553). The

current emphasis is on opening the recruitment infra-structures, which is ongoing, and in developing the monitoring infrastructure. No patient has yet been included, and expected starting point of the study is December 2017.

The principle investigator (KA), the scientific expert (EF), the statistician (FF) and the study coordinator (AR) will write the first draft of the manuscript. All the co-authors (investigators who had realized not less than 30 inclusions) will append and approve the final manuscript before the submission. No professional writer will be used.

In conclusion, the PACMAN trial is an investigator-initiated randomized controlled trial powered to test the hypothesis that the short-course of moderate doses of dexamethasone in patients undergoing major non-cardiac surgery decreases the risk of post-operative complications. The results of the PACMAN Trial will be relevant to the wide number of clinicians interested in perioperative medicine.

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AUTHORS' CONTRIBUTIONS
KA, EF, FF and AR conceived the study, coordinated its design and drafted the manuscript. AR and KA wrote the manuscript. EF and FF read and were involved in critical appraisal and revision of the manuscript. FF provided statistical expertise. All authors approved the final manuscript prior to submission.

COMPETING INTERESTS
No competing interests

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DATA SHARING STATEMENT
The principal investigator will have access to the trial data set. Patient level data and/or full dataset and/or statistical code will be available on request to the corresponding author. Consent was not obtained, but the presented data are anonymised and risk of identification is low and the potential benefits of sharing these data outweigh the potential harms.

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List of abbreviations

DSMB: Data and Safety Monitoring Board, ICU: Intensive Care Unit, ITT: Intention-to-treat.

Competing interests

The authors declare that they have no competing interests.

Figure 1: Flow chart.

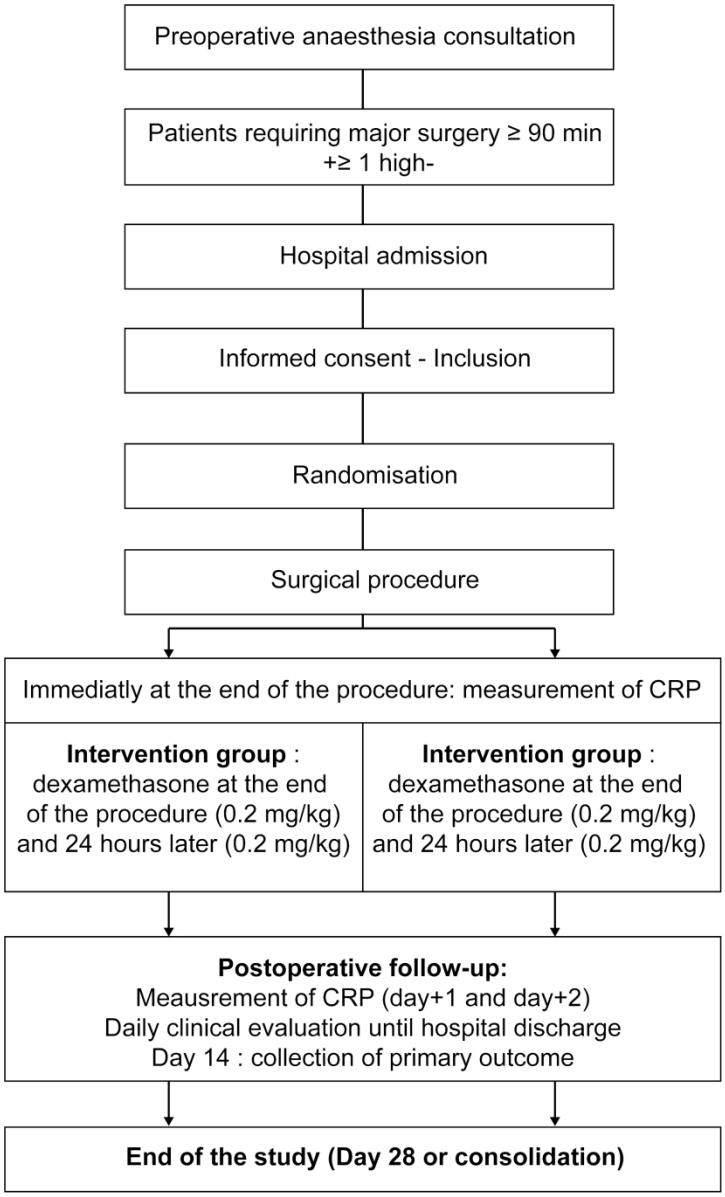

Figure 1

173x289mm (300 x 300 DPI)

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The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery: a randomized, multicentre, double blind, superiority study

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The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery: a randomized, multicentre, double blind, superiority study

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Key words: surgery; glucocorticoid; dexamethasone; post-operative complications; pneumonia

ABSTRACT

Introduction Postoperative complications are major healthcare problems and are associated with a reduced short-term and long-term survival after surgery. An excessive postoperative inflammatory response participates to the development of postoperative infection and mortality. The aim of the PACMAN study is to assess the effectiveness of perioperative administration of corticosteroid to reduce postoperative morbidity and mortality in patients undergoing major non-cardiac surgery.

Methods and analysis: The PACMAN is a multicentre, randomized, controlled, double blind, superiority, two-arms trial of 1222 high-risk patients aged 50 years of older undergoing major non-cardiac surgery at 32 acute care hospital in France. Patients are randomly assigned to dexamethasone (0,2mg.kg-1 at the end of the surgical procedure, and at day+1, n=611) or to placebo (n=611). The primary outcome is a composite of predefined 14-day major pulmonary complications and mortality. Secondary outcomes are surgical complications, infections, organ failures, critical care–free days, length of hospital stay and all-cause mortality at 28 days.

Ethics and dissemination: The PACMAN trial protocol has been approved by the ethics committee of Sud Mediterranée V, and will be carried out according to the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The PACMAN trial is the first randomized controlled trial powered to investigate whether perioperative administration of corticosteroids in patients undergoing non-cardiac major surgery reduce postoperative complications. The results of this study will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

Trial registration number clinicaltrials.gov NCT03218553

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is a multicenter, randomized, controlled and double blind trial adequately powered to determine whether corticosteroid reduces postoperative complications in high risk patients undergoing major non-cardiac surgery.
- Treatment's benefits include reduced risk of postoperative infection, development of organ failure and reduced risk of mortality.
- Limitations due to the difficulty of sepsis diagnosis after major surgery are limited by the use of a placebo ensuring a double-blind evaluation of the primary outcome.
- This large study has the potential of changing international recommendations on the management of high risk patients undergoing major non-cardiac surgery.

INTRODUCTION

More than 300 million major surgical procedures are undertaken worldwide each year [1]. For most patients, risks of surgery are low. However in an European international cohort, the mortality rate for patients undergoing non-cardiac surgery was higher than excepted (4% of patients died before hospital discharge) [2]. It is interesting to consider that 10% of patients at risk of postoperative complications represent 80% of postoperative deaths [3]. It is also important to consider that patients who develop complications but survive until hospital discharge have usually reduced functional independence and long-term survival [4]. These data suggest that interventions to prevent complications and mortality should probably be undertaken early. One of the main targets to focus on is probably lung. Indeed, postoperative respiratory complications represent the most common perioperative complication after wound infections with an estimated incidence ranging from 2.0% to 5.6% for surgical procedures [4]. Respiratory failure after general anaesthesia and tracheal extubation has been shown to be one of the most meaningful factors associated with poor patient outcomes, leading to longer hospital stay [4]. Considering, the high volume of surgical procedures undertaken each year, the key message is that decreasing even a low rate of avoidable harm will be associated with a high cost saving for the society and many preventable deaths and complications for the patients.

Major surgery induces an inflammatory response characterized by activation of platelets, neutrophils, monocytes, macrophages, cascades (coagulation, fibrinolytic, and kallikrein). The consequences of tissue surgical injuries are a release of danger-associated molecular patterns which initiate the production of pro-inflammatory mediators (cytokines, radical oxygen species) [5]. This inflammatory response is useful for tissue healing, but it is thought that an excessive response contributes to post-operative morbidity (such as infections and organ failures) and mortality. Glucocorticoids have thus been proposed to reduce the risk of complications in several medical conditions characterized by systemic inflammatory response.

In patients undergoing major cardiac surgery, corticosteroids were associated with reduction in length of intensive care unit stay [6], but a beneficial effect on the risk of mortality is uncertain [7]. In severe trauma patients, considering the potential immunostimulating effects of “low doses” corticosteroids [8], we have shown, in two multicentre, randomized, double blind placebo-controlled study on intubated trauma patients, that the use of an intravenous low-dose corticosteroids, compared with placebo, resulted in a decreased risk of hospital- acquired pneumonia [9,10]. Interestingly, apart from higher insulin consumption in patients receiving corticosteroids, no significant harm related to treatment was recorded in both studies. In major non-cardiac surgery, a recent meta-analysis concluded that perioperative administration of glucocorticoids is safe, but proofs are lacking to demonstrate clinically important benefits [11]. The

objective of the PACMAN study is to ascertain whether or not the administration of early corticosteroid with standard care compared with standard care alone prevents respiratory complications and reduces mortality in high-risk patients undergoing major surgery. We are reporting the version 4 of the protocol (2nd September 2017). This manuscript has been submitted for publication on the 30th of November 2017, before the inclusion of the first patient in the study.

Methods and Design

Hypothesis

High-risk patients treated with short course of corticosteroid have reduced morbidity and mortality rates compared to those receiving standard care alone after major non-cardiac surgery.

Research Questions

1. Does short-course of moderate doses of dexamethasone prevent death and/or post-operative respiratory complications after major non-cardiac surgery in high-risk patients ?
2. Does short-course of moderate doses of dexamethasone reduce the duration of hospitalization after major non-cardiac surgery in high-risk patients ?
3. Does short-course of moderate doses of dexamethasone prevent delayed skin healing ?

Design

The Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac surgery (PACMAN) study is a multicenter, randomized, double blind, parallel-group, superiority, controlled trial (Figure 1).

Ethic

The Institutional Review Board of Sud Mediterranée V (France) approved the study protocol (June 2017). Patients provide written consent for participation. The PACMAN trial is conducted in accordance with the declaration of Helsinki and is registered on June 2017 at http://clinicaltrial.gov/ with trial registration NCT03218553.

Setting

The study involved 33 French hospitals, each centre caring for more than 200 patients undergoing major surgery each year.

Study population

Investigators screen consecutive high-risk patients undergoing major non-cardiac surgery. Patients older than 50 years and scheduled for a major surgery (> 90 minutes and performed under general anesthesia) of the abdomen, pelvis, thorax, face/neck, vascular surgery are eligible provided that they have one or more of the following risk factors : age > 65 years, presence of a defined risk factor for cardiac or respiratory disease (exercise tolerance equivalent to 6 metabolic equivalents or less), medical history of stroke, moderate to severe renal impairment (clearance of creatinine ≤ 30 mll/L), active smoking, averaged observed blood losses over 500 ml or emergency surgery. These risk factors have been adapted from the systematic review for the preoperative pulmonary risk

stratification for non-cardiothoracic surgery published by the American College of Physicians [12] and from the guidelines for the management of severe perioperative bleeding of the European Society of Anesthesiology [13]. Exclusions criteria are: allergy to the intravenous formulation of dexamethasone, treatment with systemic corticosteroids at a dose > 5 $mg.day^{-1}$ of equivalent prednisolone in the previous 3 months, uncontrolled psychotic disorder (acute or chronical) chronic renal failure (clearance of creatinine < 10 ml/min), life expectancy of less than 1 month, preoperative shock (defined by the need for continuous infusion of vasoactive drugs (norepinephrine, epinephrine or dobutamine), acute pulmonary edema in the last 7 days, active bacterial or viral infection, pregnant women, breastfeeding women, minors, Adults under guardianship or trusteeship.

Identification and information of patients

All consecutive adult patients requiring surgery with an expected duration ≥ 90 minutes will be assessed for eligibility. During the anesthesia consultation or in the operating room in case of emergency surgery, local investigators (anesthesiologists and/or surgeons) will verify inclusion and exclusion criteria. Investigators will invite the patients to participate to the study. Patients will be informed in complete and faithful terms and in understandable language of the objectives and constraints of the study, the potential risks, the required observation and safety measures, and their right to refuse to participate in the study or to revoke their consent at any time. All information appears in an information notice and consent form given to the patient. Written informed consent will be obtained by the investigator. All these documents are approved by the competent Ethics Committee. Two original copies will be co-signed by both the investigator and the patient and the parents. The second copy is to be kept in the patient's medical record.

Treatment Allocation

Patients are randomized in a 1:1 ratio and stratified according to cancer (yes/no) and according to the type of surgical procedure (thoracic surgery or not). Randomisation is made by a computerized number generator list provided by a statistician not involved in the determination of eligibility or in the assessment of outcomes. All assignments are made through a dedicated, pass-word protected, SSL-encrypted website. Patients are randomized in the first 24 prior to surgery to dexamethasone (intervention group) or to placebo (control group).

Masking protocol

Randomized patients are given a number corresponding to a «PACMAN treatment pack» that contains: 4 x 10 mg vial of dexamethasone or placebo, and a sheet for schedule administration.

Procedures

At the end of the surgery (< 2 hours after skin closure), and before study drug administration, the blood level of c-reactive protein (CRP) is measured (Figure 1). Then, patients randomized to either slow intravenous infusion of dexamethasone (0.2 $mg.kg^{-1}$ of real body-weight within the 2 hours after the end of the surgery, and at day+1) or injection of placebo receive treatment (Figure 1). The blood level of CRP is measured at day+1 and day+2 after surgery. The treatment is administrated slowly (over 15 to 30 minutes) independently of the CRP levels.

Standard of care

According to recent recommendations and publications, clinicians are prompted to realise adequate timing of antimicrobial prophylaxis [14], to apply a protective ventilation strategy (low tidal volume and Positive End Expiratory Pressure) during surgery [15], to closely monitor and treat peroperative hypovolemia and hypotension [16,17] and to early stop sedation at the end of the surgery [18]. Decisions of post-operative admission to intensive care unit and of prophylactic application of non-invasive ventilation will follow local standard of cares. Prophylactic administration of glucocorticoid for postoperative nausea and vomiting or postoperative oedema is not permitted. Clinicians can use glucocorticoid during the first 7 days of the study only in case of formal indication of steroid such as stridor (rescue therapy).

Protocol drop-out

For patients developing an allergic reaction to the study treatment, the second injection will not be performed and the appropriate treatment of the allergic reaction will be provided. Patients with allergic reaction to dexamethasone will be kept in analysis and remain analysis with the intervention group. Patients treated with out-of-protocol glucocorticoid will be kept in analysis and remain analysis with their attributed group.

Study end points

The primary outcome is a composite outcome (all-cause mortality and major postoperative complications) within 14 days after surgery, at least one item among the following: postoperative sepsis, Postoperative pulmonary complication (postoperative pneumonia, need for invasive ventilation and/or noninvasive ventilation for respiratory failure) and all-cause mortality. The rates of patients discharged before day 14, and evaluated between day 14 and day 28, will be reported.

Secondary outcomes are all-cause mortality at 28 days, duration of invasive mechanical ventilation, duration of non-invasive mechanical ventilation, hospital free-days at 28 days, surgical complications according to the Clavien-Dindo classification within 28 days, unplanned admission or readmission to intensive care units (within 28 days following randomization), organ failures within 14 days after surgery, Sequential Organ Failure Assessment (SOFA) at day+1 and day+3, proportion of patients who experienced adverse events, especially hyperglycaemia, healing impairment, anastomotic leakage at day +14 after surgery.

Follow-up Data

The following variables are collected: demographics, American Society of Anesthesiology (ASA) score, pre-operative medical optimization, per-surgery management (drugs, mechanical ventilation, durations of procedure, fluid infusion, bleeding, post-operative analgesia), infections, organ failures, blood levels of CRP, healing, post-operative complications (including anastomotic leakage), length of ventilator support, and ICU hospitalisation and death at day 28 are recorded.

Data Collection and Checking

Data will be entered into the electronic web-based (Clinsight) case report form (eCRF) by trial or clinical personnel under the supervision of the study site investigators. From the eCRFs the trial database will be established.

Study Monitoring

The study will be monitored on behalf of the promotor (Nantes University Hospital). Site staff will be available to facilitate the monitoring visits and ensure that all required documentation is available for review. Study initiation visits are carried out at all sites before recruitment starts at that site. During regular monitoring visits realized throughout the duration of the trial, an independent research assistant will carry out Source Data Verification of trial data, verify informed consent forms and ensure the completeness of the Investigator Site Files.

Study Oversight

Study sponsor is the Nantes University Hospital (5 allée de l'ile Gloriette, 44000 Nantes, drc-nantes@chu-nantes.fr). Experienced research staff will monitor the study for quality, the integrity of data in all the participating centers. Serious adverse events and unexpected related or possibly related serious events are reported blinded to the promotor within respectively 24 hours or 7 days. An independent data and safety monitoring board (DSMB) is appointed by the sponsor. The DSMB is made up of 4 individuals with no connection to the research, including three clinician specializing in the management of ICU patients and corticotherapy in ICU, and a methodologist/biostatistician. Before the first inclusion, and every 300 inclusions, the DSMB looks over the ethics in accordance with the Declaration of Helsinki, monitors patient safety and reviews safety issues as the study progresses. The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions

- to permanently terminate the research in light of serious adverse reactions.
- to recommend increasing the total number of patients to be included to ensure the study power in case of high number of exclusions in the per-protocol analysis.

The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the research. Trial recruitment can be stopped by the promotor on the advice of the DSMB in case of safety concern.

Roles of the sponsor and of the funder

The sponsor and the funder have no role in the design or conduct of the study, the data analysis, the writing of the manuscript or in the decision to submit the manuscript.

Statistical consideration

All analyses will be performed with the use of SAS software (version 9.4, NC, USA) before the breaking of the randomization code, according to International Conference on Harmonization-Good Clinical Practice guidelines. Analyzes will be conducted, first, on data from the modified intention-to-treat (modified-ITT) population, second, in the intention-to-treat (ITT) population as well as in the per-protocol population. The criteria for including patients in the modified-ITT and in the per-protocol populations, respectively, are provided below.

Continuous variables will be presented as mean and standard deviations (as median and quartiles, otherwise) and will be compared with the use of the unpaired *t* test or the Mann-Whitney *U* test when appropriate. The Shapiro-Wilk test will be used to assess normality, and the Fisher-Snedecor test to assess homoscedasticity. Categorical data will be presented as exact numbers and percentages.

Number of patients

The rate of the primary endpoint in the control group is expected to reach 20% [15,19]. Assuming a 20% rate in the control group and 14% in the dexamethasone group, A total of 1222 patients are needed to detect this difference between the two groups with a 5% type I error and a power of 80% in a two-sided test.

Pre-Planned primary analysis

For the primary analysis, data will be analysed with the use of logistic regression adjusted for stratification factors (cancer and thoracic procedure).

The effects of the treatment will be investigated in ITT, in modified-ITT and in per-protocol populations. **In the ITT analyse,** all randomized patients will be kept in analysis. In the **modified-ITT analyse,** all randomized patients will be kept in analysis except those who would not have been eligible for randomization according to the inclusion/non-inclusion criteria or those who have not received any injection of the experimental treatment (dexamethasone or placebo). In the **per-protocol analyse,** all randomized patients will be kept in analysis except patients having one or

more major protocol violations defined as those who would not be eligible for randomization according to inclusion/non-inclusion criteria; or those who accidentally would have received the wrong intervention (Dexamethasone or placebo); or those in whom surgical intervention could not have been done (for example, intra-abdominal extensive cancer); or those who have withdrawn consent; those who would have received out-of-protocol glucocorticoids.

Pre-specified sub-group analyses:

- Strates of randomization (cancer yes/no, thoracic procedure yes/no)
- Medical history of corticosteroid in the preceding 3 months (yes/no)
- Emergency *vs* scheduled surgery
- According to the level of CRP measured at the end of the surgical procedure immediately before the first injection of the studied treatment (< 50, 50-150 or > 150 mg/mL).
- According to the surgery (abdomen, pelvis, thorax, face/neck or vascular surgery)
- In diabetic and non-diabetic patients.

No interim efficacy analyze will be performed so that no adjustment is required to the final p-value to allow for the multiple testing. The DSMB will only analyse safety data and can make recommendation for adjustment of the number of patients to be included to ensure the statistical power of the mITT analysis.

Method for missing data

There should not be missing data for the primary outcome measure and the missing data rate should be low for the other outcomes as well. Missing data will be described by treatment arm. According to the rate of missing data (over 5%) sensitivity analyses will be performed using multiple imputation methods as well as worst case scenario (missing data considered as the most unfavourable case) and maximum bias scenario (missing data considered as the most favourable or unfavourable case in the placebo and experimental arms respectively).

Data Sharing statement

The principle investigator will have access to the final trial data set. Data sharing: patient level data and/or full dataset and/or statistical code will be available upon request to the corresponding author. Consent for the data sharing was not obtained but the presented data are anonymised and risk of identification is low and the potential benefits of sharing these data outweigh the potential harms.

Patient and Public Involvement statement

The development of the research question and outcome measures was informed by patients' priorities, which is notably the prevention of post-operative complications. Patients were not involved neither in the design of the study. Patients were involved neither in the recruitment nor in the conduct of the study. Results of the study will be disseminated to study participants upon personal request to the study coordinator. For this randomised clinical trial, the burden of the

intervention was assessed by an institutional review board, notably composed of representative of patient associations.

DISCUSSION

The PACMAN trial is a nationwide randomized controlled study powered to investigate short-course of moderate dose of dexamethasone in patients undergoing major non-cardiac surgery.

Several trials have investigated the benefits of administering corticosteroids in patients undergoing major surgery. However, there is yet no agreement on the beneficial effects of corticosteroids in alleviating surgical stress. This disagreement probably stems from the variability in the drugs used, their dosage and administration schedule, and the surgical procedures in different studies. Also the fear of side effects induced by a possible immunosuppression (infections, postoperative wound complications, anastomotic leakage) explains the extreme variability of behaviour from one centre to another and among patients and physicians. These considerations prevented the performance of a large scale randomized study despite evidences that corticosteroids could enhance outcome and even decrease the rate of infections after non-cardiac major surgery (see above). Before general recommendations for perioperative corticosteroids administration can be made, obviously conclusive safety studies must be available. So far, there seem to be no safety issues [20-22] related to a single preoperative dose of corticosteroids including specific studies on wound healing [23,24]. The consequences of perioperative use of corticosteroids for glucose homeostasis need further evaluation, but so far the transitory increased hyperglycemic response has not been related to increased postoperative complications [25]. To reach definitive conclusion on the effects of glucocorticoids on the risk of post-operative infections, we are eagerly awaiting the results from the PADDI randomized clinical trial which is investigating the effects of low dose of dexamethasone on surgical site infection, and from the PACMAN trial whose primary outcome is a composite outcome made of death and respiratory infections.

While perioperative glucocorticoids are widely administrated, the latest meta-analyses found that we are lacking power to detect differences in complications [11], and that no definitive conclusions can be made regarding clinically important benefice [7]. While the PADDI study is a non-inferiority trial designed to test the safety of dexamethasone in an unselected population, we have designed the PACMAN trial to investigate the potential benefits of the treatment in a surgical population with high risk of post-operative respiratory complications according to American and European recommendations [12,13]. Risk factors of pulmonary complications are either related to the surgery, or to the medical history of the patients. The external validity of the PACMAN results

to unselected patients should be cautious in case of increased risks of the side-effects recorded as secondary outcomes.

We decided to not limit the PACMAN study to a specific type of surgery but to include all sort of surgery provided that the expected duration of the procedure exceeds 90 minutes. This strategy maximises recruitment rates and improves the generalisation of results. We acknowledge that the clinical risk factors of postoperative respiratory complications are inconstantly used in clinical practice, which can limit the applicability to the study results. However, preoperative optimization by nutritional support, respiratory physiotherapy or smoking cessation are recommended in patients presenting such risk factors [12]. The selection of high risk patients will result in a high incidence rate of the primary endpoint, which will result in a study of high clinical relevance and statistical power.

A wide range of doses of dexamethasone has been tested in surgical or critically ill patients : from low (4-8 mg/day [11,26]), to high doses (1-2 mg/kg [6,27]). The PACMAN trial is designed to investigate the effects of dexamethasone on the risk of major respiratory complications, notably pneumonia, and we thus decided to evaluate the effects of moderate doses as proposed in the latest recommendations and meta-analysis for the treatment with steroids of in patients with pneumonia [28,29]. The timing of administration is also critical to consider. We decided to initiate the study treatment during the post-operative inflammatory response, rather than before the surgery, because glucocorticoids induce the apoptosis of immune cells in absence of inflammation but are stimulate immunity when administrated during an inflammatory response [30,31].

We selected a composite outcome as the primary criteria. The use of mortality as a primary endpoint is never used in perioperative studies because the risk of death is low and the statistical power would be low. Respiratory complications are particularly frequent and serious after major surgery and we have recently proposed that glucocorticoid prevent the development of inflammation-related immunosuppression [8], and decrease the risk of pneumonia after severe trauma [9,10]. Finally, mortality is not competitive with the primary criteria since the outcome all cause of death is included in the composite primary outcome.

For the primary statistical analysis of the primary outcome, we will use a modified intention to treat analysis including patients fulfilling all the inclusion criteria and who have received at least one injection of the experimental treatment. This strategy has recently been used in randomized clinical trials evaluating peri-procedure treatments [17,32], because the time between the randomization, which is realized before the procedure, and the administration of the study treatment, which is realized during or after the procedure, expose the study to a high risk of

included patients not receiving the allocated treatment (e.g. cancelled or delayed surgery or perioperative complications). In this setting, we strongly believe that the mITT is more accurate to the medical field than the ITT. However, the exclusion of patients in the mITT analysis can theoretically decrease the statistical power of the study. Thus, the DSMB will have access to the number of patients excluded from the miTT analysis, and if necessary the DMSB will have the responsibility to propose an increase of the number of patients to be included to guarantee the study power. Finally, the intention-to-treat analysis will be reported in the final version of the manuscript.

Trial status

The trial has already achieved many milestones. The trial is sponsored by the French ministry of health (PHRCN 2016_0442). Insurance for non-negligent harm has been provided by University Hospital of Nantes (France). Research ethics committee approval was obtained in September 2019 (Comité de Protection des Personnes Sud Méditerranée V). The French Agency for the safety of medicines and medical devices authorized the study in September 2017 (#170245RS-21). The study is registered with the American registry of trials (https://clinicaltrials.gov/ NCT03218553). The current emphasis is on opening the recruitment infra-structures, which is ongoing, and in developing the monitoring infrastructure. No patient has yet been included, and expected starting point of the study is December 2017.

The principle investigator (KA), the scientific expert (EF), the statistician (FF) and the study coordinator (AR) will write the first draft of the manuscript. All the co-authors (investigators who had realized not less than 30 inclusions) will append and approve the final manuscript before the submission. No professional writer will be used.

In conclusion, the PACMAN trial is an investigator-initiated randomized controlled trial powered to test the hypothesis that the short-course of moderate doses of dexamethasone in patients undergoing major non-cardiac surgery decreases the risk of post-operative complications. The results of the PACMAN Trial will be relevant to the wide number of clinicians interested in perioperative medicine.

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AUTHORS' CONTRIBUTIONS

KA, EF, FF and AR conceived the study, coordinated its design and drafted the manuscript. AR and KA wrote the manuscript. EF and FF read and were involved in critical appraisal and revision of the

manuscript. FF provided statistical expertise. All authors approved the final manuscript prior to submission.

COMPETING INTERESTS

No competing interests

SOURCE OF FUNDING

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DATA SHARING STATEMENT

The principal investigator will have access to the trial data set. Patient level data and/or full dataset and/or statistical code will be available on request to the corresponding author. Consent was not obtained, but the presented data are anonymised and risk of identification is low and the potential benefits of sharing these data outweigh the potential harms.

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List of abbreviations

DSMB: Data and Safety Monitoring Board, ICU: Intensive Care Unit, ITT: Intention-to-treat.

Competing interests

The authors declare that they have no competing interests.

Figure 1: Flow chart.

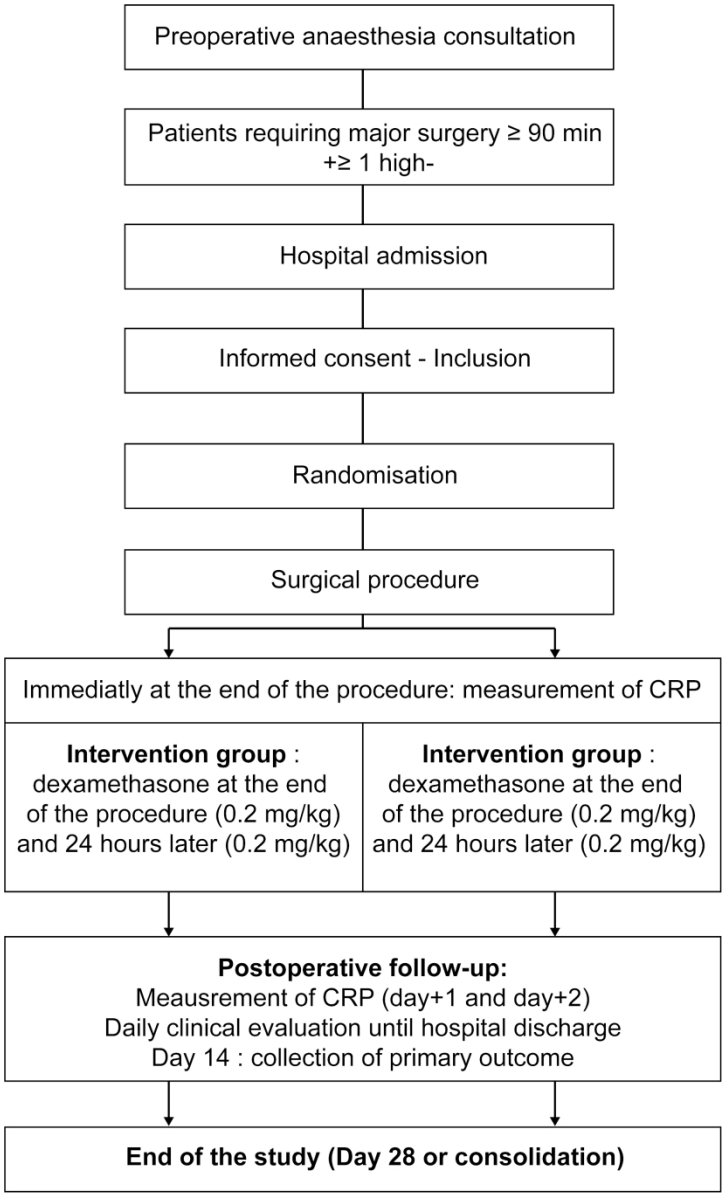

Figure 1

173x289mm (300 x 300 DPI)

BMJ Open

The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery: a randomized, multicentre, double blind, superiority study

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The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery: a randomized, multicentre, double blind, superiority study

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Key words: surgery; glucocorticoid; dexamethasone; post-operative complications; pneumonia

ABSTRACT

Introduction Postoperative complications are major healthcare problems and are associated with a reduced short-term and long-term survival after surgery. An excessive postoperative inflammatory response participates to the development of postoperative infection and mortality. The aim of the PACMAN study is to assess the effectiveness of perioperative administration of corticosteroid to reduce postoperative morbidity and mortality in patients undergoing major non-cardiac surgery.

Methods and analysis: The PACMAN is a multicentre, randomized, controlled, double blind, superiority, two-arms trial of 1222 high-risk patients aged 50 years of older undergoing major non-cardiac surgery at 32 acute care hospital in France. Patients are randomly assigned to dexamethasone (0,2mg.kg-1 at the end of the surgical procedure, and at day+1, n=611) or to placebo (n=611). The primary outcome is a composite of predefined 14-day major pulmonary complications and mortality. Secondary outcomes are surgical complications, infections, organ failures, critical care–free days, length of hospital stay and all-cause mortality at 28 days.

Ethics and dissemination: The PACMAN trial protocol has been approved by the ethics committee of Sud Mediterranée V, and will be carried out according to the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The PACMAN trial is a randomized controlled trial powered to investigate whether perioperative administration of corticosteroids in patients undergoing non-cardiac major surgery reduce postoperative complications. The results of this study will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

Trial registration number clinicaltrials.gov NCT03218553

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is a multicenter, randomized, controlled and double blind trial adequately powered to determine whether corticosteroid reduces postoperative complications in high risk patients undergoing major non-cardiac surgery.
- Potential treatment's benefits include reduced risk of postoperative infection, development of organ failure and reduced risk of mortality.
- Limitations due to the difficulty of sepsis diagnosis after major surgery are limited by the use of a placebo ensuring a double-blind evaluation of the primary outcome.
- This large study has the potential of changing international recommendations on the management of high risk patients undergoing major non-cardiac surgery.

INTRODUCTION

More than 300 million major surgical procedures are undertaken worldwide each year [1]. For most patients, risks of surgery are low. However in an European international cohort, the mortality rate for patients undergoing non-cardiac surgery was higher than excepted (4% of patients died before hospital discharge) [2]. It is interesting to consider that 10% of patients at risk of postoperative complications represent 80% of postoperative deaths [3]. It is also important to consider that patients who develop complications but survive until hospital discharge have usually reduced functional independence and long-term survival [4]. These data suggest that interventions to prevent complications and mortality should probably be undertaken early. One of the main targets to focus on is probably lung. Indeed, postoperative respiratory complications represent the most common perioperative complication after wound infections with an estimated incidence ranging from 2.0% to 5.6% for surgical procedures [4]. Respiratory failure after general anaesthesia and tracheal extubation has been shown to be one of the most meaningful factors associated with poor patient outcomes, leading to longer hospital stay [4]. Considering, the high volume of surgical procedures undertaken each year, the key message is that decreasing even a low rate of avoidable harm will be associated with a high cost saving for the society and many preventable deaths and complications for the patients.

Major surgery induces an inflammatory response characterized by activation of platelets, neutrophils, monocytes, macrophages, cascades (coagulation, fibrinolytic, and kallikrein). The consequences of tissue surgical injuries are a release of danger-associated molecular patterns which initiate the production of pro-inflammatory mediators (cytokines, radical oxygen species) [5]. This inflammatory response is useful for tissue healing, but it is thought that an excessive response contributes to post-operative morbidity (such as infections and organ failures) and mortality. Glucocorticoids have thus been proposed to reduce the risk of complications in several medical conditions characterized by systemic inflammatory response.

In patients undergoing major cardiac surgery, corticosteroids were associated with reduction in length of intensive care unit stay [6], but no difference in 30 day mortality or major morbidity in was found [7]. In severe trauma patients, considering the potential immunostimulating effects of “low doses” corticosteroids [8], we have shown, in two multicentre, randomized, double blind placebo-controlled study on intubated trauma patients, that the use of an intravenous low-dose corticosteroids, compared with placebo, resulted in a decreased risk of hospital- acquired pneumonia [9,10]. Interestingly, apart from higher insulin consumption in patients receiving corticosteroids, no significant

harm related to treatment was recorded in both studies. In major non-cardiac surgery, a recent meta-analysis concluded that proofs are lacking to demonstrate clinically important benefits with perioperative administration of glucocorticoids, and that safety has not been sufficiently investigated to rule out any clinically important side effects [11]. The objective of the PACMAN study is to ascertain whether or not the administration of early corticosteroid with standard care compared with standard care alone prevents respiratory complications and reduces mortality in high-risk patients undergoing major surgery. We are reporting the version 4 of the protocol (2nd September 2017). This manuscript has been submitted for publication on the 30th of November 2017, before the inclusion of the first patient in the study.

Methods and Design

Hypothesis

High-risk patients treated with short course of corticosteroid have reduced morbidity and mortality rates compared to those receiving standard care alone after major non-cardiac surgery.

Research Questions

1. Does short-course of moderate doses of dexamethasone prevent death and/or post-operative respiratory complications after major non-cardiac surgery in high-risk patients ?
2. Does short-course of moderate doses of dexamethasone reduce the duration of hospitalization after major non-cardiac surgery in high-risk patients ?
3. Does short-course of moderate doses of dexamethasone prevent delayed skin healing ?

Design

The Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac surgery (PACMAN) study is a multicenter, randomized, double blind, parallel-group, superiority, controlled trial (Figure 1).

Ethic

The Institutional Review Board of Sud Mediterranée V (France) approved the study protocol (June 2017). Patients provide written consent for participation. The PACMAN trial is conducted in accordance with the declaration of Helsinki and is registered on June 2017 at http://clinicaltrial.gov/ with trial registration NCT03218553.

Setting

The study involved 33 French hospitals, each centre caring for more than 200 patients undergoing major surgery each year.

Study population

Investigators screen consecutive high-risk patients undergoing major non-cardiac surgery. Patients older than 50 years and scheduled for a major surgery (> 90 minutes and performed under general anesthesia) of the abdomen, pelvis, thorax, face/neck, vascular surgery are eligible provided that they have one or more of the following risk factors : age > 65 years, presence of a defined risk factor for cardiac or respiratory disease (exercise tolerance equivalent to 6 metabolic equivalents or less), medical

history of stroke, moderate to severe renal impairment (clearance of creatinine ≤ 30 mll/L), active smoking, averaged observed blood losses over 500 ml or emergency surgery. These risk factors have been adapted from the systematic review for the preoperative pulmonary risk stratification for non-cardiothoracic surgery published by the American College of Physicians [12] and from the guidelines for the management of severe perioperative bleeding of the European Society of Anesthesiology [13]. Exclusions criteria are: allergy to the intravenous formulation of dexamethasone, treatment with systemic corticosteroids at a dose > 5 $mg.day^{-1}$ of equivalent prednisolone in the previous 3 months, uncontrolled psychotic disorder (acute or chronical) chronic renal failure (clearance of creatinine < 10 ml/min), life expectancy of less than 1 month, preoperative shock (defined by the need for continuous infusion of vasoactive drugs (norepinephrine, epinephrine or dobutamine), acute pulmonary edema in the last 7 days, active bacterial or viral infection, pregnant women, breastfeeding women, minors, Adults under guardianship or trusteeship.

Identification and information of patients

All consecutive adult patients requiring surgery with an expected duration ≥ 90 minutes will be assessed for eligibility. During the anesthesia consultation or in the operating room in case of emergency surgery, local investigators (anesthesiologists and/or surgeons) will verify inclusion and exclusion criteria. Investigators will invite the patients to participate to the study. Patients will be informed in complete and faithful terms and in understandable language of the objectives and constraints of the study, the potential risks, the required observation and safety measures, and their right to refuse to participate in the study or to revoke their consent at any time. All information appears in an information notice and consent form given to the patient. Written informed consent will be obtained by the investigator. All these documents are approved by the competent Ethics Committee. Two original copies will be co-signed by both the investigator and the patient and the parents. The second copy is to be kept in the patient's medical record.

Treatment Allocation

Patients are randomized in a 1:1 ratio and stratified according to cancer (yes/no) and according to the type of surgical procedure (thoracic surgery or not). Randomisation is made by a computerized number generator list provided by a statistician not involved in the determination of eligibility or in the assessment of outcomes. All assignments are made through a dedicated, pass-word protected, SSL-encrypted website. Patients are randomized in the first 24 prior to surgery to dexamethasone (intervention group) or to placebo (control group).

Masking protocol

Randomized patients are given a number corresponding to a «PACMAN treatment pack» that contains: 4 x 10 mg vial of dexamethasone or placebo, and a sheet for schedule administration.

Procedures

At the end of the surgery (< 2 hours after skin closure), and before study drug administration, the blood level of c-reactive protein (CRP) is measured (Figure 1). Then, patients randomized to either slow intravenous infusion of dexamethasone (0.2 $mg.kg^{-1}$ of real body-weight within the 2 hours after the end of the surgery, and at day+1) or injection of placebo receive treatment (Figure 1). The blood level of CRP is measured at day+1 and day+2 after surgery. The treatment is administrated slowly (over 15 to 30 minutes) independently of the CRP levels.

Standard of care

According to recent recommendations and publications, clinicians are prompted to realise adequate timing of antimicrobial prophylaxis [14], to apply a protective ventilation strategy (low tidal volume and Positive End Expiratory Pressure) during surgery [15], to closely monitor and treat peroperative hypovolemia and hypotension [16,17] and to early stop sedation at the end of the surgery [18]. Decisions of post-operative admission to intensive care unit and of prophylactic application of non-invasive ventilation will follow local standard of cares. Prophylactic administration of glucocorticoid for postoperative nausea and vomiting or postoperative oedema is not permitted. Clinicians can use glucocorticoid during the first 7 days of the study only in case of formal indication of steroid such as stridor (rescue therapy).

Protocol drop-out

For patients developing an allergic reaction to the study treatment, the second injection will not be performed and the appropriate treatment of the allergic reaction will be provided. Patients with allergic reaction to dexamethasone will be kept in analysis and remain analysis with the intervention group. Patients treated with out-of-protocol glucocorticoid will be kept in analysis and remain analysis with their attributed group.

Study end points

The primary outcome is a composite outcome (all-cause mortality and major postoperative complications) within 14 days after surgery, at least one item among the following: postoperative sepsis, Postoperative pulmonary complication (postoperative pneumonia, need for invasive ventilation and/or noninvasive ventilation for respiratory failure) and all-cause mortality.

The diagnosis of pneumonia will be retained according to European guidelines i.e. association 48 hours after admission of at least 2 signs (body temperature > 38°C; leukocytosis >12 000/mL, or leukopenia <4000/mL; purulent pulmonary secretions) with the appearance of a new infiltrate or change in an existing infiltrate on chest x-ray and a bacterial documentation (blood or respiratory fluid analysis) [19,20].

The rates of patients discharged before day 14, and evaluated between day 14 and day 28, will be reported. Secondary outcomes are all-cause mortality at 28 days, duration of invasive mechanical ventilation, duration of non-invasive mechanical ventilation, hospital free-days at 28 days, surgical complications according to the Clavien-Dindo classification within 28 days, unplanned admission or readmission to intensive care units (within 28 days following randomization), organ failures within 14 days after surgery, Sequential Organ Failure Assessment (SOFA) at day+1 and day+3, proportion of patients who experienced adverse events, especially hyperglycaemia, healing impairment, anastomotic leakage at day +14 after surgery.

Follow-up Data

The following variables are collected: demographics, American Society of Anesthesiology (ASA) score, pre-operative medical optimization, per-surgery management (drugs, mechanical ventilation, durations of procedure, fluid infusion, bleeding, post-operative analgesia), infections, organ failures, blood levels of CRP, healing, post-operative complications (including anastomotic leakage), length of ventilator support, and ICU hospitalisation and death at day 28 are recorded.

Data Collection and Checking

Data will be entered into the electronic web-based (Clinsight) case report form (eCRF) by trial or clinical personnel under the supervision of the study site investigators. From the eCRFs the trial database will be established.

Study Monitoring

The study will be monitored on behalf of the promotor (Nantes University Hospital). Site staff will be available to facilitate the monitoring visits and ensure that all required documentation is available for review. Study initiation visits are carried out at all sites before recruitment starts at that site. During regular monitoring visits realized throughout the duration of the trial, an independent research assistant will carry out Source Data Verification of trial data, verify informed consent forms and ensure the completeness of the Investigator Site Files.

Study Oversight

Study sponsor is the Nantes University Hospital (5 allée de l'ile Gloriette, 44000 Nantes, drc-nantes@chu-nantes.fr). Experienced research staff will monitor the study for quality, the integrity of data in all the participating centers. Serious adverse events and unexpected related or possibly related serious events are reported blinded to the promotor within respectively 24 hours or 7 days. An independent data and safety monitoring board (DSMB) is appointed by the sponsor. The DSMB is made up of 4 individuals with no connection to the research, including three clinician specializing in the management of ICU patients and corticotherapy in ICU, and a methodologist/biostatistician. Before the first inclusion, and every 300 inclusions, the DSMB looks over the ethics in accordance with the Declaration of Helsinki, monitors patient safety and reviews safety issues as the study progresses. The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the research in light of serious adverse reactions.
- to recommend increasing the total number of patients to be included to ensure the study power in case of high number of exclusions in the per-protocol analysis.

The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the research. Trial recruitment can be stopped by the promotor on the advice of the DSMB in case of safety concern.

Roles of the sponsor and of the funder

The sponsor and the funder have no role in the design or conduct of the study, the data analysis, the writing of the manuscript or in the decision to submit the manuscript.

Statistical consideration

All analyses will be performed with the use of SAS software (version 9.4, NC, USA) before the breaking of the randomization code, according to International Conference on Harmonization-Good Clinical Practice guidelines. Analyzes will be conducted, first, on data from the modified intention-to-treat (modified-ITT) population, second, in the intention-to-treat (ITT) population as well as in the per-protocol population. The criteria for including patients in the modified-ITT and in the per-protocol populations, respectively, are provided below.

Continuous variables will be presented as mean and standard deviations (as median and quartiles, otherwise) and will be compared with the use of the unpaired *t* test or the Mann-Whitney *U* test when appropriate. The Shapiro-Wilk test will be used to assess normality, and the Fisher-Snedecor test to assess homoscedasticity. Categorical data will be presented as exact numbers and percentages.

Number of patients

The rate of the primary endpoint in the control group is expected to reach 20% [15,21]. Assuming a 20% rate in the control group and 14% in the dexamethasone group, A total of 1222 patients are needed to detect this difference between the two groups with a 5% type I error and a power of 80% in a two-sided test.

Pre-Planned primary analysis

For the primary analysis, data will be analysed with the use of logistic regression adjusted for stratification factors (cancer and thoracic procedure).

The effects of the treatment will be investigated in ITT, in modified-ITT and in per-protocol populations. **In the ITT analyse,** all randomized patients will be kept in analysis. In the **modified-ITT analyse,** all randomized patients will be kept in analysis except those who would not have been eligible for randomization according to the inclusion/non-inclusion criteria or those who have not received any injection of the experimental treatment (dexamethasone or placebo). In the **per-protocol analyse,** all randomized patients will be kept in analysis except patients having one or more major protocol violations defined as those who would not be eligible for randomization according to inclusion/non-inclusion criteria; or those who accidentally would have received the wrong intervention (Dexamethasone or placebo); or those in whom surgical intervention could not have been done (for example, intra-abdominal extensive cancer); or those who have withdrawn consent; those who would have received out-of-protocol glucocorticoids.

Pre-specified exploratory sub-group analyses:

- Strates of randomization (cancer yes/no, thoracic procedure yes/no)
- Medical history of corticosteroid in the preceding 3 months (yes/no)
- Emergency *vs* scheduled surgery
- According to the level of CRP measured at the end of the surgical procedure immediately before the first injection of the studied treatment (< 50, 50-150 or > 150 mg/mL).
- According to the surgery (abdomen, pelvis, thorax, face/neck or vascular surgery)
- In diabetic and non-diabetic patients.

No interim efficacy analyze will be performed so that no adjustment is required to the final p-value to allow for the multiple testing. The DSMB will only analyse safety data and can make

recommendation for adjustment of the number of patients to be included to ensure the statistical power of the mITT analysis.

Method for missing data

There should not be missing data for the primary outcome measure and the missing data rate should be low for the other outcomes as well. Missing data will be described by treatment arm. According to the rate of missing data (over 5%) sensitivity analyses will be performed using multiple imputation methods as well as worst case scenario (missing data considered as the most unfavourable case) and maximum bias scenario (missing data considered as the most favourable or unfavourable case in the placebo and experimental arms respectively).

Data Sharing statement

The principle investigator will have access to the final trial data set. Data sharing: patient level data and/or full dataset and/or statistical code will be available upon request to the corresponding author. Consent for the data sharing was not obtained but the presented data are anonymised and risk of identification is low and the potential benefits of sharing these data outweigh the potential harms.

Patient and Public Involvement statement

The development of the research question and outcome measures was informed by patients' priorities, which is notably the prevention of post-operative complications. Patients were not involved neither in the design of the study. Patients were involved neither in the recruitment nor in the conduct of the study. Results of the study will be disseminated to study participants upon personal request to the study coordinator. For this randomised clinical trial, the burden of the intervention was assessed by an institutional review board, notably composed of representative of patient associations.

DISCUSSION

The PACMAN trial is a nationwide randomized controlled study powered to investigate short-course of moderate dose of dexamethasone in patients undergoing major non-cardiac surgery.

Several trials have investigated the benefits of administering corticosteroids in patients undergoing major surgery. However, there is yet no agreement on the beneficial effects of corticosteroids in alleviating surgical stress. This disagreement probably stems from the variability in the drugs used, their dosage and administration schedule, and the surgical procedures in different studies. Also the fear of side effects induced by a possible immunosuppression (infections, postoperative wound complications, anastomotic leakage) explains the extreme variability of behaviour from one centre to

another and among patients and physicians. These considerations prevented the performance of a large scale randomized study despite evidences that corticosteroids could enhance outcome and even decrease the rate of infections after non-cardiac major surgery (see above). Before general recommendations for perioperative corticosteroids administration can be made, obviously conclusive safety studies must be available. So far, there seem to be no safety issues [22-24] related to a single preoperative dose of corticosteroids including specific studies on wound healing [25,26]. The consequences of perioperative use of corticosteroids for glucose homeostasis need further evaluation, but so far the transitory increased hyperglycemic response has not been related to increased postoperative complications [27]. To reach definitive conclusion on the effects of glucocorticoids on the risk of post-operative infections, we are eagerly awaiting the results from the PADDI randomized clinical trial which is investigating the effects of low dose of dexamethasone on surgical site infection, and from the PACMAN trial whose primary outcome is a composite outcome made of death and respiratory infections.

While perioperative glucocorticoids are widely administrated, the latest meta-analyses found that we are lacking power to detect differences in complications [11], and that no definitive conclusions can be made regarding clinically important benefice [7]. While the PADDI study is a non-inferiority trial designed to test the safety of dexamethasone in an unselected population, we have designed the PACMAN trial to investigate the potential benefits of the treatment in a surgical population with high risk of post-operative respiratory complications according to American and European recommendations [12,13]. Risk factors of pulmonary complications are either related to the surgery, or to the medical history of the patients. The external validity of the PACMAN results to unselected patients should be cautious in case of increased risks of the side-effects recorded as secondary outcomes.

We decided to not limit the PACMAN study to a specific type of surgery but to include all sort of surgery provided that the expected duration of the procedure exceeds 90 minutes. This strategy maximises recruitment rates and improves the generalisation of results. We acknowledge that the clinical risk factors of postoperative respiratory complications are inconstantly used in clinical practice, which can limit the applicability to the study results. However, preoperative optimization by nutritional support, respiratory physiotherapy or smoking cessation are recommended in patients presenting such risk factors [12]. The selection of high risk patients will result in a high incidence rate of the primary endpoint, which will result in a study of high clinical relevance and statistical power.

A wide range of doses of dexamethasone has been tested in surgical or critically ill patients : from low (4-8 mg/day [11,28]), to high doses (1-2 mg/kg [6,29]). The PACMAN trial is designed to investigate the effects of dexamethasone on the risk of major respiratory complications, notably

pneumonia, and we thus decided to evaluate the effects of moderate doses as proposed in the latest recommendations and meta-analysis for the treatment with steroids of in patients with pneumonia [30,31]. The timing of administration is also critical to consider. We decided to initiate the study treatment during the post-operative inflammatory response, rather than before the surgery, because glucocorticoids induce the apoptosis of immune cells in absence of inflammation but are stimulate immunity when administrated during an inflammatory response [32,33].

We selected a composite outcome as the primary criteria. The use of mortality as a primary endpoint is never used in perioperative studies because the risk of death is low and the statistical power would be low. Respiratory complications are particularly frequent and serious after major surgery and we have recently proposed that glucocorticoid prevent the development of inflammation-related immunosuppression [8], and decrease the risk of pneumonia after severe trauma [9,10]. Finally, mortality is not competitive with the primary criteria since the outcome all cause of death is included in the composite primary outcome.

For the primary statistical analysis of the primary outcome, we will use a modified intention to treat analysis including patients fulfilling all the inclusion criteria and who have received at least one injection of the experimental treatment. This strategy has recently been used in randomized clinical trials evaluating peri-procedure treatments [17,34], because the time between the randomization, which is realized before the procedure, and the administration of the study treatment, which is realized during or after the procedure, expose the study to a high risk of included patients not receiving the allocated treatment (e.g. cancelled or delayed surgery or perioperative complications). In this setting, we strongly believe that the mITT is more accurate to the medical field than the ITT. However, the exclusion of patients in the mITT analysis can theoretically decrease the statistical power of the study. Thus, the DSMB will have access to the number of patients excluded from the miTT analysis, and if necessary the DMSB will have the responsibility to propose an increase of the number of patients to be included to guarantee the study power. Finally, the intention-to-treat analysis will be reported in the final version of the manuscript.

Trial status

The trial has already achieved many milestones. The trial is sponsored by the French ministry of health (PHRCN 2016_0442). Insurance for non-negligent harm has been provided by University Hospital of Nantes (France). Research ethics committee approval was obtained in September 2019 (Comité de Protection des Personnes Sud Méditerranée V). The French Agency for the safety of medicines and medical devices authorized the study in September 2017 (#170245RS-21). The study is

registered with the American registry of trials (https://clinicaltrials.gov/ NCT03218553). The current emphasis is on opening the recruitment infra-structures, which is ongoing, and in developing the monitoring infrastructure. No patient has yet been included, and expected starting point of the study is December 2017.

The principle investigator (KA), the scientific expert (EF), the statistician (FF) and the study coordinator (AR) will write the first draft of the manuscript. All the co-authors (investigators who had realized not less than 30 inclusions) will append and approve the final manuscript before the submission. No professional writer will be used.

In conclusion, the PACMAN trial is an investigator-initiated randomized controlled trial powered to test the hypothesis that the short-course of moderate doses of dexamethasone in patients undergoing major non-cardiac surgery decreases the risk of post-operative complications. The results of the PACMAN Trial will be relevant to the wide number of clinicians interested in perioperative medicine.

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AUTHORS' CONTRIBUTIONS
KA, EF, FF and AR conceived the study, coordinated its design and drafted the manuscript. AR and KA wrote the manuscript. EF and FF read and were involved in critical appraisal and revision of the manuscript. FF provided statistical expertise. All authors approved the final manuscript prior to submission.

COMPETING INTERESTS
No competing interests

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DATA SHARING STATEMENT
The principal investigator will have access to the trial data set. Patient level data and/or full dataset and/or statistical code will be available on request to the corresponding author. Consent was not obtained, but the presented data are anonymised and risk of identification is low and the potential benefits of sharing these data outweigh the potential harms.

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List of abbreviations

DSMB: Data and Safety Monitoring Board, ICU: Intensive Care Unit, ITT: Intention-to-treat.

Competing interests

The authors declare that they have no competing interests.

Figure 1: Flow chart.

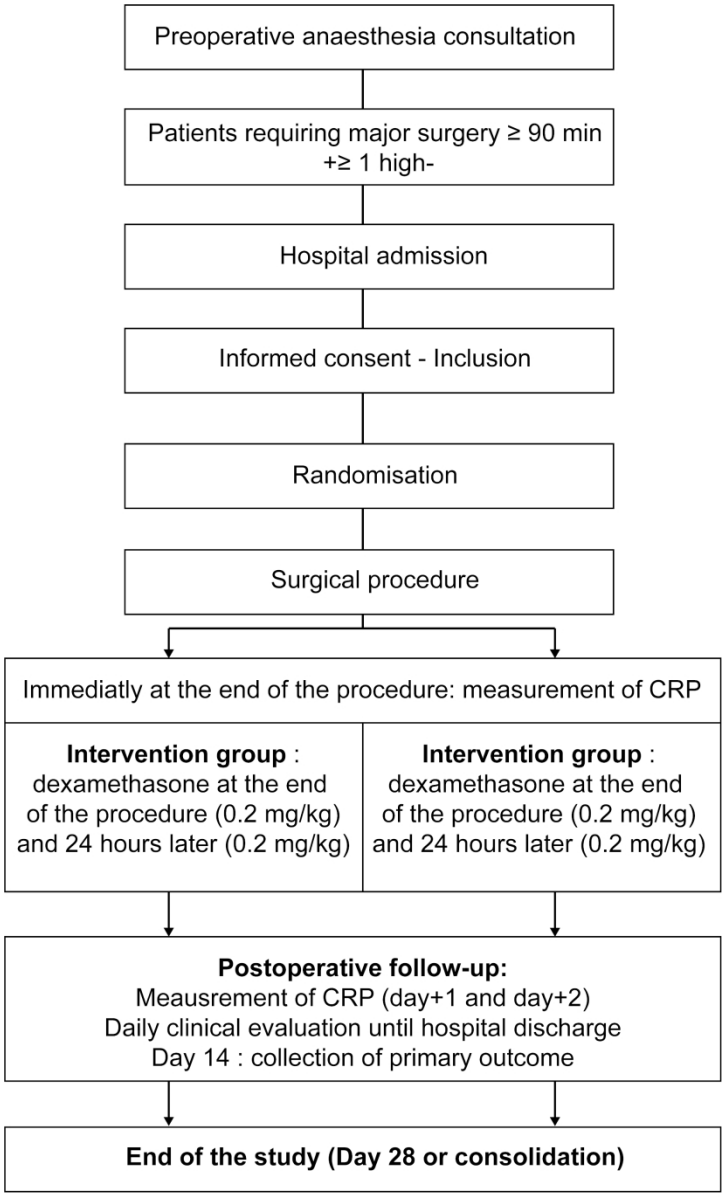

Figure 1

173x289mm (300 x 300 DPI)

BMJ Open

The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery: a randomized, multicentre, double blind, superiority study

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The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery: a randomized, multicentre, double blind, superiority study

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ABSTRACT

Introduction Postoperative complications are major healthcare problems and are associated with a reduced short-term and long-term survival after surgery. An excessive postoperative inflammatory response participates to the development of postoperative infection and mortality. The aim of the PACMAN study is to assess the effectiveness of perioperative administration of corticosteroid to reduce postoperative morbidity and mortality in patients undergoing major non-cardiac surgery.

Methods and analysis: The PACMAN is a multicentre, randomized, controlled, double blind, superiority, two-arm trial of 1222 high-risk patients aged 50 years or older undergoing major non-cardiac surgery at 32 acute care hospital in France. Patients are randomly assigned to dexamethasone (0,2mg.kg^{-1} at the end of the surgical procedure, and at day+1, n=611) or to placebo (n=611). The primary outcome is a composite of predefined 14-day major pulmonary complications and mortality. Secondary outcomes are surgical complications, infections, organ failures, critical care–free days, length of hospital stay and all-cause mortality at 28 days.

Ethics and dissemination: The PACMAN trial protocol has been approved by the ethics committee of Sud Mediterranée V, and will be carried out according to the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The PACMAN trial is a randomized controlled trial powered to investigate whether perioperative administration of corticosteroids in patients undergoing non-cardiac major surgery reduce postoperative complications. The results of this study will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

Trial registration number clinicaltrials.gov NCT03218553

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is a multicenter, randomized, controlled and double blind trial adequately powered to determine whether corticosteroid reduces postoperative complications in high risk patients undergoing major non-cardiac surgery.
- Potential treatment's benefits include reduced risk of postoperative infection, development of organ failure and reduced risk of mortality.
- Limitations due to the difficulty of sepsis diagnosis after major surgery are limited by the use of a placebo ensuring a double-blind evaluation of the primary outcome.
- This large study has the potential of changing international recommendations on the management of high risk patients undergoing major non-cardiac surgery.

INTRODUCTION

More than 300 million major surgical procedures are undertaken worldwide each year [1]. For most patients, risks of surgery are low. However in an European international cohort, the mortality rate for patients undergoing non-cardiac surgery was higher than excepted (4% of patients died before hospital discharge) [2]. It is interesting to consider that 10% of patients at risk of postoperative complications represent 80% of postoperative deaths [3]. It is also important to consider that patients who develop complications but survive until hospital discharge have usually reduced functional independence and long-term survival [4]. These data suggest that interventions to prevent complications and mortality should probably be undertaken early. One of the main targets to focus on is probably lung. Indeed, postoperative respiratory complications represent the most common perioperative complication after wound infections with an estimated incidence ranging from 2.0% to 5.6% for surgical procedures [4]. Respiratory failure after general anaesthesia and tracheal extubation has been shown to be one of the most meaningful factors associated with poor patient outcomes, leading to longer hospital stay [4]. Considering, the high volume of surgical procedures undertaken each year, the key message is that decreasing even a low rate of avoidable harm will be associated with a high cost saving for the society and many preventable deaths and complications for the patients.

Major surgery induces an inflammatory response characterized by activation of platelets, neutrophils, monocytes, macrophages, cascades (coagulation, fibrinolytic, and kallikrein). The consequences of tissue surgical injuries are a release of danger-associated molecular patterns which initiate the production of pro-inflammatory mediators (cytokines, radical oxygen species) [5]. This inflammatory response is useful for tissue healing, but it is thought that an excessive response contributes to post-operative morbidity (such as infections and organ failures) and mortality. Glucocorticoids have thus been proposed to reduce the risk of complications in several medical conditions characterized by systemic inflammatory response.

In patients undergoing major cardiac surgery, corticosteroids were associated with reduction in length of intensive care unit stay [6], but no difference in 30 day mortality or major morbidity in was found [7]. In severe trauma patients, considering the potential immunostimulating effects of “low doses” corticosteroids [8], we have shown, in two multicentre, randomized, double blind placebo-controlled study on intubated trauma patients, that the use of an intravenous low-dose corticosteroids, compared with placebo, resulted in a decreased risk of hospital- acquired pneumonia [9,10]. Interestingly, apart from higher insulin consumption in patients receiving corticosteroids, no significant harm related to treatment was recorded in both studies. In major non-cardiac surgery, a recent meta-analysis concluded that proofs are lacking to demonstrate clinically

important benefits with perioperative administration of glucocorticoids, and that safety has not been sufficiently investigated to rule out any clinically important side effects [11]. The objective of the PACMAN study is to ascertain whether or not the administration of early corticosteroid with standard care compared with standard care alone prevents respiratory complications and reduces mortality in high-risk patients undergoing major surgery. We are reporting the version 4 of the protocol (2nd September 2017). This manuscript has been submitted for publication on the 30th of November 2017, before the inclusion of the first patient in the study.

Methods and Design

Hypothesis

High-risk patients treated with short course of corticosteroid have reduced morbidity and mortality rates compared to those receiving standard care alone after major non-cardiac surgery.

Research Questions

1. Does short-course of moderate doses of dexamethasone prevent death and/or post-operative respiratory complications after major non-cardiac surgery in high-risk patients ?
2. Does short-course of moderate doses of dexamethasone reduce the duration of hospitalization after major non-cardiac surgery in high-risk patients ?
3. Does short-course of moderate doses of dexamethasone prevent delayed skin healing ?

Design

The Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac surgery (PACMAN) study is a multicenter, randomized, double blind, parallel-group, superiority, controlled trial (Figure 1). KA and AR wrote the first draft of the protocol. FF was responsible of the statistical plan. EF extensively revised the protocol. All the authors approved the final version.

Ethic approval

The Institutional Review Board of Sud Mediterranée V (France) approved the study protocol (June 2017, version 4). Patients provide written consent for participation (see supplementary file). The PACMAN trial is conducted in accordance with the declaration of Helsinki and is registered on June 2017 at http://clinicaltrial.gov/ with trial registration NCT03218553.

Setting

The study involved 33 French hospitals, each centre caring for more than 200 patients undergoing major surgery each year.

Study population

Investigators screen consecutive high-risk patients undergoing major non-cardiac surgery. Patients older than 50 years and scheduled for a major surgery (> 90 minutes and performed under general anesthesia) of the abdomen, pelvis, thorax, face/neck, vascular surgery are eligible provided that they have one or more of the following risk factors : age > 65 years, presence of a defined risk factor for cardiac or respiratory disease (exercise tolerance equivalent to 6 metabolic equivalents or less), medical history of stroke, moderate to severe renal impairment (clearance of creatinine ≤ 30

mll/L), active smoking, averaged observed blood losses over 500 ml or emergency surgery. These risk factors have been adapted from the systematic review for the preoperative pulmonary risk stratification for non-cardiothoracic surgery published by the American College of Physicians [12] and from the guidelines for the management of severe perioperative bleeding of the European Society of Anesthesiology [13]. Exclusions criteria are: allergy to the intravenous formulation of dexamethasone, treatment with systemic corticosteroids at a dose > 5 $mg.day^{-1}$ of equivalent prednisolone in the previous 3 months, uncontrolled psychotic disorder (acute or chronical) chronic renal failure (clearance of creatinine < 10 ml/min), life expectancy of less than 1 month, preoperative shock (defined by the need for continuous infusion of vasoactive drugs (norepinephrine, epinephrine or dobutamine), acute pulmonary edema in the last 7 days, active bacterial or viral infection, pregnant women, breastfeeding women, minors, Adults under guardianship or trusteeship.

Identification and information of patients

All consecutive adult patients requiring surgery with an expected duration ≥ 90 minutes will be assessed for eligibility. During the anesthesia consultation or in the operating room in case of emergency surgery, local investigators (anesthesiologists and/or surgeons) will verify inclusion and exclusion criteria. Investigators will invite the patients to participate to the study. Patients will be informed in complete and faithful terms and in understandable language of the objectives and constraints of the study, the potential risks, the required observation and safety measures, and their right to refuse to participate in the study or to revoke their consent at any time. All information appears in an information notice and consent form given to the patient. Written informed consent will be obtained by the investigator. All these documents are approved by the competent Ethics Committee. Two original copies will be co-signed by both the investigator and the patient and the parents. The second copy is to be kept in the patient's medical record.

Treatment Allocation

Patients are randomized in a 1:1 ratio and stratified according to cancer (yes/no) and according to the type of surgical procedure (thoracic surgery or not). Randomisation is made by a computerized number generator list provided by a statistician not involved in the determination of eligibility or in the assessment of outcomes. All assignments are made through a dedicated, pass-word protected, SSL-encrypted website. Patients are randomized in the first 24 prior to surgery to dexamethasone (intervention group) or to placebo (control group).

Masking protocol

Randomized patients are given a number corresponding to a «PACMAN treatment pack» that contains: 4 x 10 mg vial of dexamethasone or , and a sheet for schedule administration.

Procedures

At the end of the surgery (< 2 hours after skin closure), and before study drug administration, the blood level of c-reactive protein (CRP) is measured (Figure 1). Then, patients randomized to either slow intravenous infusion of dexamethasone (0.2 $mg.kg^{-1}$ of real body-weight within the 2 hours after the end of the surgery, and at day+1) or injection of placebo receive treatment (Figure 1). The blood level of CRP is measured at day+1 and day+2 after surgery. The treatment is administrated slowly (over 15 to 30 minutes) independently of the CRP levels.

Standard of care

According to recent recommendations and publications, clinicians are prompted to realise adequate timing of antimicrobial prophylaxis [14], to apply a protective ventilation strategy (low tidal volume and Positive End Expiratory Pressure) during surgery [15], to closely monitor and treat peroperative hypovolemia and hypotension [16,17] and to early stop sedation at the end of the surgery [18]. Decisions of post-operative admission to intensive care unit and of prophylactic application of non-invasive ventilation will follow local standard of cares. Prophylactic administration of glucocorticoid for postoperative nausea and vomiting or postoperative oedema is not permitted. Clinicians can use glucocorticoid during the first 7 days of the study only in case of formal indication of steroid such as stridor (rescue therapy).

Protocol drop-out

For patients developing an allergic reaction to the study treatment, the second injection will not be performed and the appropriate treatment of the allergic reaction will be provided. Patients with allergic reaction to dexamethasone will be kept in analysis and remain analysis with the intervention group. Patients treated with out-of-protocol glucocorticoid will be kept in analysis and remain analysis with their attributed group. No procedure for revealing a participant's allocated intervention during the trial is planned.

Study end points

The primary outcome is a composite outcome (all-cause mortality and major postoperative complications) within 14 days after surgery, at least one item among the following: postoperative sepsis, Postoperative pulmonary complication (postoperative pneumonia, need for invasive ventilation and/or noninvasive ventilation for respiratory failure) and all-cause mortality.

The diagnosis of pneumonia will be retained according to European guidelines i.e. association 48 hours after admission of at least 2 signs (body temperature > 38°C; leukocytosis >12 000/mL, or leukopenia <4000/mL; purulent pulmonary secretions) with the appearance of a new infiltrate or change in an existing infiltrate on chest x-ray and a bacterial documentation (blood or respiratory fluid analysis) [19,20].

The rates of patients discharged before day 14, and evaluated between day 14 and day 28, will be reported. Secondary outcomes are all-cause mortality at 28 days, duration of invasive mechanical ventilation, duration of non-invasive mechanical ventilation, hospital free-days at 28 days, surgical complications according to the Clavien-Dindo classification within 28 days, unplanned admission or readmission to intensive care units (within 28 days following randomization), organ failures within 14 days after surgery, Sequential Organ Failure Assessment (SOFA) at day+1 and day+3, proportion of patients who experienced adverse events, especially hyperglycaemia, healing impairment, anastomotic leakage at day +14 after surgery.

Follow-up Data

The following variables are collected: demographics, American Society of Anesthesiology (ASA) score, pre-operative medical optimization, per-surgery management (drugs, mechanical ventilation, durations of procedure, fluid infusion, bleeding, post-operative analgesia), infections, organ failures, blood levels of CRP, healing, post-operative complications (including anastomotic leakage), length of ventilator support, and ICU hospitalisation and death at day 28 are recorded.

Data Collection and Checking

Data will be entered into the electronic web-based (Clinsight) case report form (eCRF) by trial or clinical personnel under the supervision of the study site investigators. From the eCRFs the trial database will be established.

Study Monitoring

The study will be monitored on behalf of the promotor (Nantes University Hospital). Site staff will be available to facilitate the monitoring visits and ensure that all required documentation is available for review. Study initiation visits are carried out at all sites before recruitment starts at that site. During regular monitoring visits realized throughout the duration of the trial, an independent research assistant will carry out Source Data Verification of trial data, verify informed consent forms and ensure the completeness of the Investigator Site Files.

Study Oversight

Study sponsor is the Nantes University Hospital (5 allée de l'ile Gloriette, 44000 Nantes, drc-nantes@chu-nantes.fr). Experienced research staff will monitor the study for quality, the integrity of data in all the participating centers. Serious adverse events and unexpected related or possibly related serious events are reported blinded to the promotor within respectively 24 hours or 7 days. An independent data and safety monitoring board (DSMB) is appointed by the sponsor. The DSMB is made up of 4 individuals with no connection to the research, including three clinician specializing in the management of ICU patients and corticotherapy in ICU, and a methodologist/biostatistician.

Before the first inclusion, and every 600 inclusions, the DSMB looks over the ethics in accordance with the Declaration of Helsinki, monitors patient safety and reviews safety issues as the study progresses. The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the research in light of serious adverse reactions.
- to recommend increasing the total number of patients to be included to ensure the study power in case of high number of exclusions in the per-protocol analysis.

The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the research. Trial recruitment can be stopped by the promotor on the advice of the DSMB in case of safety concern.

Roles of the sponsor and of the funder

The sponsor and the funder have no role in the design or conduct of the study, the data analysis, the writing of the manuscript or in the decision to submit the manuscript.

Statistical consideration

All analyses will be performed with the use of SAS software (version 9.4, NC, USA) before the breaking of the randomization code, according to International Conference on Harmonization-Good Clinical Practice guidelines. Analyzes will be conducted, first, on data from the modified intention-to-treat (modified-ITT) population, second, in the intention-to-treat (ITT) population as well as in the per-protocol population. The criteria for including patients in the modified-ITT and in the per-protocol populations, respectively, are provided below.

Continuous variables will be presented as mean and standard deviations (as median and quartiles, otherwise) and will be compared with the use of the unpaired *t* test or the Mann-Whitney *U* test when appropriate. The Shapiro-Wilk test will be used to assess normality, and the Fisher-Snedecor test to assess homoscedasticity. Categorical data will be presented as exact numbers and percentages.

Number of patients

The rate of the primary endpoint in the control group is expected to reach 20% [15,21]. Assuming a 20% rate in the control group and 14% in the dexamethasone group, A total of 1222 patients are needed to detect this difference between the two groups with a 5% type I error and a power of 80% in a two-sided test.

Pre-Planned primary analysis

For the primary analysis, data will be analysed with the use of logistic regression adjusted for stratification factors (cancer and thoracic procedure).

The effects of the treatment will be investigated in ITT, in modified-ITT and in per-protocol populations. **In the ITT analyse,** all randomized patients will be kept in analysis. In the **modified-ITT analyse,** all randomized patients will be kept in analysis except those who would not have been eligible for randomization according to the inclusion/non-inclusion criteria or those who have not received any injection of the experimental treatment (dexamethasone or placebo). In the **per-protocol analyse,** all randomized patients will be kept in analysis except patients having one or more major protocol violations defined as those who would not be eligible for randomization according to inclusion/non-inclusion criteria; or those who accidentally would have received the wrong intervention (Dexamethasone or placebo); or those in whom surgical intervention could not have been done (for example, intra-abdominal extensive cancer); or those who have withdrawn consent; those who would have received out-of-protocol glucocorticoids.

Pre-specified exploratory sub-group analyses:

- Strates of randomization (cancer yes/no, thoracic procedure yes/no)
- Medical history of corticosteroid in the preceding 3 months (yes/no)
- Emergency *vs* scheduled surgery
- According to the level of CRP measured at the end of the surgical procedure immediately before the first injection of the studied treatment (< 50, 50-150 or > 150 mg/mL).
- According to the surgery (abdomen, pelvis, thorax, face/neck or vascular surgery)
- In diabetic and non-diabetic patients.

No interim efficacy analyze will be performed so that no adjustment is required to the final p-value to allow for the multiple testing. The DSMB will only analyse safety data and can make recommendation for adjustment of the number of patients to be included to ensure the statistical power of the mITT analysis. Important protocol modificationswill be disseminate by the promotors to all the relevant parties.

Method for missing data

There should not be missing data for the primary outcome measure and the missing data rate should be low for the other outcomes as well. Missing data will be described by treatment arm. According to the rate of missing data (over 5%) sensitivity analyses will be performed using multiple imputation methods as well as worst case scenario (missing data considered as the most unfavourable case) and maximum bias scenario (missing data considered as the most favourable or unfavourable case in the placebo and experimental arms respectively).

Data Sharing statement

The principle investigator will have access to the final trial data set. Data sharing: patient level data and/or full dataset and/or statistical code will be available upon request to the corresponding author. Consent for the data sharing was not obtained but the presented data are anonymised and risk of identification is low and the potential benefits of sharing these data outweigh the potential harms.

Patient and Public Involvement statement

The development of the research question and outcome measures was informed by patients' priorities, which is notably the prevention of post-operative complications. Patients were not involved neither in the design of the study. Patients were involved neither in the recruitment nor in the conduct of the study. Results of the study will be disseminated to study participants upon personal request to the study coordinator. For this randomised clinical trial, the burden of the intervention was assessed by an institutional review board, notably composed of representative of patient associations.

DISCUSSION

The PACMAN trial is a nationwide randomized controlled study powered to investigate short-course of moderate dose of dexamethasone in patients undergoing major non-cardiac surgery.

Several trials have investigated the benefits of administering corticosteroids in patients undergoing major surgery. However, there is yet no agreement on the beneficial effects of corticosteroids in alleviating surgical stress. This disagreement probably stems from the variability in the drugs used, their dosage and administration schedule, and the surgical procedures in different studies. Also the fear of side effects induced by a possible immunosuppression (infections, postoperative wound complications, anastomotic leakage) explains the extreme variability of behaviour from one centre to another and among patients and physicians. These considerations prevented the performance of a large scale randomized study despite evidences that corticosteroids could enhance outcome and even decrease the rate of infections after non-cardiac major surgery (see above). Before general recommendations for perioperative corticosteroids administration can be made, obviously conclusive safety studies must be available. So far, there seem to be no safety issues [22-24] related to a single preoperative dose of corticosteroids including specific studies on wound healing [25,26]. The consequences of perioperative use of corticosteroids for glucose homeostasis need further evaluation, but so far the transitory increased hyperglycemic response has not been related to increased postoperative complications [27]. To reach definitive conclusion on the effects of glucocorticoids on the risk of post-operative infections, we are eagerly awaiting the results from the PADDI randomized clinical trial which is investigating the effects of low dose of

dexamethasone on surgical site infection, and from the PACMAN trial whose primary outcome is a composite outcome made of death and respiratory infections.

While perioperative glucocorticoids are widely administrated, the latest meta-analyses found that we are lacking power to detect differences in complications [11], and that no definitive conclusions can be made regarding clinically important benefice [7]. While the PADDI study is a non-inferiority trial designed to test the safety of dexamethasone in an unselected population, we have designed the PACMAN trial to investigate the potential benefits of the treatment in a surgical population with high risk of post-operative respiratory complications according to American and European recommendations [12,13]. Risk factors of pulmonary complications are either related to the surgery, or to the medical history of the patients. The external validity of the PACMAN results to unselected patients should be cautious in case of increased risks of the side-effects recorded as secondary outcomes.

We decided to not limit the PACMAN study to a specific type of surgery but to include all sort of surgery provided that the expected duration of the procedure exceeds 90 minutes. This strategy maximises recruitment rates and improves the generalisation of results. We acknowledge that the clinical risk factors of postoperative respiratory complications are inconstantly used in clinical practice, which can limit the applicability to the study results. However, preoperative optimization by nutritional support, respiratory physiotherapy or smoking cessation are recommended in patients presenting such risk factors [12]. The selection of high risk patients will result in a high incidence rate of the primary endpoint, which will result in a study of high clinical relevance and statistical power.

A wide range of doses of dexamethasone has been tested in surgical or critically ill patients : from low (4-8 mg/day [11,28]), to high doses (1-2 mg/kg [6,29]). The PACMAN trial is designed to investigate the effects of dexamethasone on the risk of major respiratory complications, notably pneumonia, and we thus decided to evaluate the effects of moderate doses as proposed in the latest recommendations and meta-analysis for the treatment with steroids of in patients with pneumonia [30,31]. The timing of administration is also critical to consider. We decided to initiate the study treatment during the post-operative inflammatory response, rather than before the surgery, because glucocorticoids induce the apoptosis of immune cells in absence of inflammation but are stimulate immunity when administrated during an inflammatory response [32,33].

We selected a composite outcome as the primary criteria. The use of mortality as a primary endpoint is never used in perioperative studies because the risk of death is low and the statistical power would be low. Respiratory complications are particularly frequent and serious after major surgery and we have recently proposed that glucocorticoid prevent the development of inflammation-related immunosuppression [8], and decrease the risk of pneumonia after severe

trauma [9,10]. Finally, mortality is not competitive with the primary criteria since the outcome all cause of death is included in the composite primary outcome.

This study has several limits. First, the primary outcome selected (composite of death, sepsis and pulmonary complications at 14 days) is biased towards the detection of benefit, as steroids are most likely to reduce pulmonary complications, but may have detrimental effects on other important outcomes e.g wound infection. This problem will be partially compensated for by the extensive secondary outcome measures being collected. Second, for the primary statistical analysis of the primary outcome, we will use a modified intention to treat analysis including patients fulfilling all the inclusion criteria and who have received at least one injection of the experimental treatment. This strategy has recently been used in randomized clinical trials evaluating peri-procedure treatments [17,34], because the time between the randomization, which is realized before the procedure, and the administration of the study treatment, which is realized during or after the procedure, expose the study to a high risk of included patients not receiving the allocated treatment (e.g. cancelled or delayed surgery or perioperative complications). In this setting, we strongly believe that the mITT is more accurate to the medical field than the ITT. However, the exclusion of patients in the mITT analysis can theoretically decrease the statistical power of the study. Thus, the DSMB will have access to the number of patients excluded from the mITT analysis, and if necessary the DMSB will have the responsibility to propose an increase of the number of patients to be included to guarantee the study power. Finally, the intention-to-treat analysis will be reported in the final version of the manuscript.

Trial status

The trial has already achieved many milestones. The trial is sponsored by the French ministry of health (PHRCN 2016_0442). Insurance for non-negligent harm has been provided by University Hospital of Nantes (France). Research ethics committee approval was obtained in September 2019 (Comité de Protection des Personnes Sud Méditerranée V). The French Agency for the safety of medicines and medical devices authorized the study in September 2017 (#170245RS-21). The study is registered with the American registry of trials (https://clinicaltrials.gov/ NCT03218553). The current emphasis is on opening the recruitment infra-structures, which is ongoing, and in developing the monitoring infrastructure. The study protocol was submitted to BMJ open before the first inclusion in the study. On December the 31st of 2018, 1050 patients have been included and randomized in the trial. The expected ending point of the study is February 2019.

The principle investigator (KA), the scientific expert (EF), the statistician (FF) and the study coordinator (AR) will write the first draft of the manuscript. All the co-authors (investigators who

had realized not less than 30 inclusions) will append and approve the final manuscript before the submission. No professional writer will be used.

In conclusion, the PACMAN trial is an investigator-initiated randomized controlled trial powered to test the hypothesis that the short-course of moderate doses of dexamethasone in patients undergoing major non-cardiac surgery decreases the risk of post-operative complications. The results of the PACMAN Trial will be relevant to the wide number of clinicians interested in perioperative medicine.

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AUTHORS' CONTRIBUTIONS

KA, EF, FF and AR conceived the study, coordinated its design and drafted the manuscript. AR and KA wrote the manuscript. EF and FF read and were involved in critical appraisal and revision of the manuscript. FF provided statistical expertise. All authors approved the final manuscript prior to submission.

COMPETING INTERESTS

No competing interests

SOURCE OF FUNDING

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DATA SHARING STATEMENT

The principal investigator will have access to the trial data set. Patient level data and/or full dataset and/or statistical code will be available on request to the corresponding author. Consent was not obtained, but the presented data are anonymised and risk of identification is low and the potential benefits of sharing these data outweigh the potential harms.

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List of abbreviations

DSMB: Data and Safety Monitoring Board, ICU: Intensive Care Unit, ITT: Intention-to-treat.

Competing interests

The authors declare that they have no competing interests.

Figure 1: Flow chart.

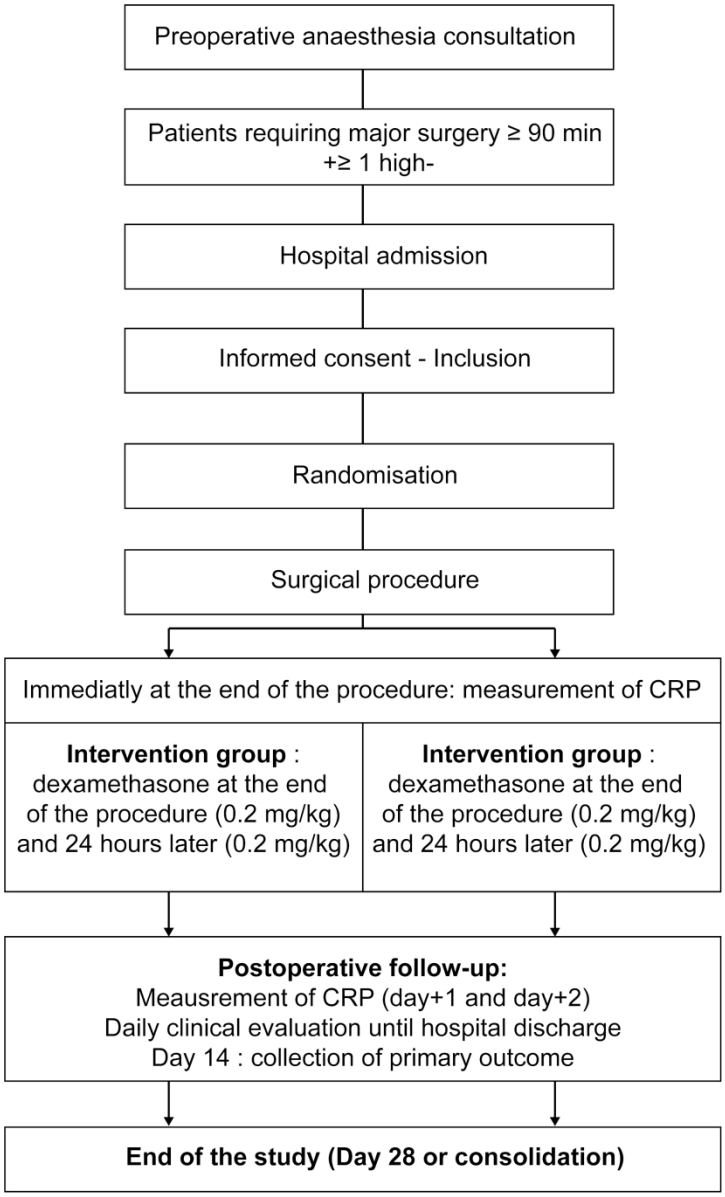

Figure 1

173x289mm (300 x 300 DPI)

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Version n° 2

Date : 16/05/2017

Attestation of consent

The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery: a randomized, multicentre, double blind, superiority study

Promotor *: CHU Nantes*

Réf : RC17_0029 *N° EudracT : 2017-000442-21*

I under-sign, Mister, Miss (first name and surname*)*……
……
……,
Date of birth: …../……/……..

Freely and voluntary accept to participate to the PACMAN study, coordinated by Prof. Karim Asehnoune and organized by CHU Nantes which acts as sponsor of the study.

Being said that :

- A medical doctor has provided clear information and responded to all my questions, has informed me that I am free to remove my consent when ever.
- I confirm that I am not under trusteeship and I am covered by medicare insurance.
- I have received a written letter precising the study aim, methodology, potential harms and benefice.
- I will have the opportunity to communicate during the study with my medical doctor,and receive informations on my health and outcomes.
- I am aware that I can withdraw my consent to participate when ever, without supporting any responsibility, but that I have to inform the doctor of my decision. The fact of discontinuing my participation to the study will alter neither my relationship with the doctors nor the quality of my cares.
- I accept that the investigators inform my generalist practitioner of my participation to this research:

  ☐ Yes ☐ No
- If I want so, at the end of the study trial, I can be informed of the final results of the study.
- My consent do not limit the responsibilities and the duties of the medical doctor and of the study promotor, and I conserve all my rights guaranteed by the Law.

- I am free to participate to other clinical research providing that the study protocol do not alter the risk of postoperative complications.
- I accept that the information recorded during this study will be electronically stored by the promotor. The right to access to my stored personal data (modified Law of January the 6th of 1978, art 39) can be exercise when ever by contacting the investigator. I thus can use my right of rectification and of opposition by informing the investigator who will be responsible to contact the study promotor. My personal data will be anonymized and will remained confidential.
- The information recorded during the study can be provided to other French or foreign searchers, providing they guarantee the same level of exigence for the protection of my personal data.
- I accept that the persons involved in the study have access to my medical files.
- I consent to the use of my medical data in the purpose of communications or publications, provided that they are anonymized.

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Version n° 2

Date : 16/05/2017

Attestation of consent

The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery: a randomized, multicentre, double blind, superiority study

Promotor *: CHU Nantes*

Réf : RC17_0029 *N° EudracT : 2017-000442-21*

Patient signature:	Date : Name and Surname :

Doctor who guarantees to have fully explain to the patient the aim, the design and the potential harms and benefits of the study research.	
Doctor signature :	Date : Name and Surname :

Signed in 2 copies : the original is to be conserved by the investigator, the copy is provided to the patient.

Doctor to contact in case of emergency : Pr Karim ASEHNOUNE

✉ Département d'Anesthésie et Réanimation, Hôtel Dieu – HME, CHU de Nantes , ☎ Tel : 0240083001 - Fax : 0240087382, Email : karim.asehnoune@chu-nantes.fr

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1 (line 1)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**3 (line 20)** **7 (line 19)** **15 (line 23)**
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	**7 (line 19)**
Funding	4	Sources and types of financial, material, and other support	**3 (line 22), 16 (line 18)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**7 (line 14)**
	5b	Name and contact information for the trial sponsor	**15 (line 18)**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**11 (line 14)**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	**From 11 (line 17) to 12 (line 12)**
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**5 (lines 25-35)**
	6b	Explanation for choice of comparators	**6 (line 3)**

Objectives	7	Specific objectives or hypotheses	**6 (line 2) 7 (line 3)**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**7**
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**7 (lines 12-14)**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**7 (line 24) to 8 (line 11)**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**9 (lines 1-17)**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**9 (lines 18-23)**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**8 (lines 31-33)**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**8 (lines 8-17)**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**9 (line 24) to 10 (line 6**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**9 (lines 2-7) and 10 (lines 7-12) + Figure 1**

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**11 (lines 28-32)**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**7 (lines 21-23)**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**8 (lines 26-29)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**8 (lines 26-29)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**8 (line 27)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**3 (line 7), 7 (line 13), 8 (lines 31-33), 9 (lines 1-7)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**9 (lines 23-24)**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**10 (lines 15-18)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**10 (lines 19-25)**

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**10 (lines 19-25)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**11 (lines 18-29) 12 (lines 1-2)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**12 (lines 14-25)**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**12 (lines 3-12)**
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**10 (lines 31- to 11 (line 14)**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**11 (lines 13-14) 12 (line 22)**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**10 (lines 29-31)**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**10 (line 31) to 11 (line 14)**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**8 (lines 17-20)**

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**12 (lines 25-26)**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**8 (lines 12-23)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**Not applicable**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**8 (lines 12-23)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**16 (line 20)**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**13 (lines 1-4)** **16 (lines 26-30)**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**Not applicable**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**3 (lines 18-20)** **16 (lines 26-30)**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**15 (line 32) to 16 (line 2)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**Not applicable**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**Supplemental File**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**Not applicable**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.