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ORIGINAL ARTICLE

Observational Study

# Physiologic postoperative presepsin kinetics following primary cementless total hip arthroplasty: A prospective observational study

Davide Bizzoca, Andrea Piazzolla, Lorenzo Moretti, Giovanni Vicenti, Biagio Moretti, Giuseppe Solarino

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**Davide Bizzoca, Andrea Piazzolla, Lorenzo Moretti,** DAI Neuroscienze, Organi di Senso e Apparato Locomotore, AOU Consorziale Policlinico di Bari, Bari 70124, Italy

**Giovanni Vicenti, Biagio Moretti, Giuseppe Solarino,** Di BraiN, University of Bari "Aldo Moro", Bari 70124, Italy

**Corresponding author:** Giuseppe Solarino, MD, PhD, Associate Professor, Di BraiN, University of Bari "Aldo Moro", Piazza Giulio Cesare, 11, Bari 70124, Italy. giuseppe.solarino@uniba.it

## Abstract

### *BACKGROUND*

Presepsin is an emerging biomarker in the diagnosis of sepsis. In the field of orthopaedics, it could be useful in diagnosing and managing periprosthetic joint infections.

### *AIM*

To define the normal postoperative presepsin plasmatic curve, in patients undergoing primary cementless total hip arthroplasty (THA).

### *METHODS*

Patients undergoing primary cementless THA at our Institute were recruited. Inclusion criteria were: Primary osteoarthritis of the hip; urinary catheter time of permanence < 24 h; peripheral venous cannulation time of permanence < 24 h; no postoperative homologous blood transfusion administration and hospital stay ≤ 8 d. Exclusion criteria were: The presence of other articular prosthetic replacement or bone fixation devices; chronic inflammatory diseases; chronic kidney diseases; history of recurrent infections or malignant neoplasms; previous surgery in the preceding 12 mo; diabetes mellitus; immunosuppressive drug or corticosteroid assumption. All the patients received the same antibiotic prophylaxis. All the THA were performed by the same surgical and anaesthesia team; total operative time was defined as the time taken from skin incision to completion of skin closure. At enrollment, anthropometric data, smocking status, osteoarthritis stage according to Kellgren and Lawrence, Harris Hip Score, drugs assumption and comorbidities were recorded. All the patients underwent serial blood tests, including complete blood count, presepsin (PS) and C-reactive protein 24 h before arthroplasty and at 24, 48, 72 and 96 h postoperatively and at 3, 6 and 12-mo follow-up.

***RESULTS***
A total of 96 patients (51 female; 45 male; mean age = 65.74 ± 5.58) were recruited. The mean PS values were: 137.54 pg/mL at baseline, 192.08 pg/mL at 24 h post-op; 254.85 pg/mL at 48 h post-op; 259 pg/mL at 72 h post-op; 248.6 pg/mL at 96-h post-op; 140.52 pg/mL at 3-mo follow-up; 135.55 pg/mL at 6-mo follow-up and 130.11 pg/mL at 12-mo follow-up. In two patients (2.08%) a soft-tissue infection was observed; in these patients, higher levels (> 350 pg/mL) were recorded at 3-mo follow-up.

***CONCLUSION***
The dosage of plasmatic PS concentration is highly recommended in patients undergoing THA before surgery to exclude the presence of an unknown infection. The PS plasmatic concentration should be also assessed at 72 h post-operatively, evaluate the maximum postoperative PS value, and at 96 h post-operatively when a decrease of presepsin should be found. The lack of a presepsin decrease at 96 h post-operatively could be a predictive factor of infection.

**Key Words:** Presepsin; Periprosthetic joint infection; Total hip arthroplasty; Total hip replacement; Hip surgery; Postoperative care



**Core Tip:** The dosage of plasmatic presepsin (PS) concentration is highly recommended in patients undergoing total hip arthroplasty before surgery to exclude the presence of an unknown infection. The PS plasmatic concentration should be also assessed at 72 h post-operatively, to evaluate the maximum postoperative PS value, and at 96 h post-operatively when a decrease of presepsin should be found. The lack of a presepsin decrease at 96 h post-operatively should be a predictive factor of infection.

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## INTRODUCTION

Periprosthetic joint infections (PJIs) are a relevant cause of prosthetic surgery revision, accounting for 15% of failed total hip arthroplasties (THA)[1-3].

PJIs are fearsome complications in orthopaedics, as they might significantly affect the patient's quality of life. Therefore, in the last two decades, an increasing interest towards the prevention of these complications has developed[1-3]. In the meantime, several research groups have investigated the potential role of presepsin (PS) in this PJI prevention and diagnosis[1-3].

PS, from a molecular point of view, is the N-terminal fragment of the soluble cluster of differentiation 14-SubType[14]. It is released into circulation after the activation of defence mechanisms, mainly bacterial phagocytosis[4].

Yaegashi *et al*[5], in 2004, hypothesized for the first time that PS could be useful as a biomarker to predict clinical prognosis in septic conditions. In the following years, different studies have highlighted the potential of PS in several infectious diseases, including severe community-acquired pneumonia, severe acute pancreatitis, infections in patients with haematological malignancies, implantable cardioverter-defibrillator (ICD) pocket infections, neonatal sepsis, pacemaker and PJIs and surgical site infections (SSIs)[6-22].

Furthermore, PS has been also studied in the risk stratification in patients undergoing cardiac surgery and as a biomarker in the perioperative management of patients undergoing total knee arthroplasty (TKA) or THA[23-29].

In a previous preliminary study, our research group defined the normal perioperative plasmatic levels of presepsin at 96 h postoperatively in 50 patients undergoing primary cementless THA and primary cemented TKA[25].

The present study aims at depicting the normal postoperative PS plasmatic curve, in patients undergoing primary cementless THA, at 12-mo follow-up.

## MATERIALS AND METHODS

### *Study population and data collection*

Patients undergoing primary cementless THA at our Institute were recruited. Ethical clearance was obtained from our centre's Clinical Research Ethics Committee, as per the 1964 Declaration of Helsinki.

All the patients gave written informed consent before enrolment in the study. Inclusion criteria were: Primary osteoarthritis of the hip; urinary catheter time of permanence < 24 h; peripheral venous cannulation time of permanence < 24 h; no postoperative homologous blood transfusion administration and hospital stay ≤ 8 d.

Exclusion criteria were: The presence of other articular prosthetic replacement or bone fixation devices; chronic inflammatory diseases; chronic kidney diseases; history of recurrent infections or malignant neoplasms; previous surgery in the preceding 12 mo; diabetes mellitus; immunosuppressive drug or corticosteroid assumption.

All the patients received the same antibiotic prophylaxis with cephazolin 2 g. All the THA were performed by the same surgical and anaesthesia team; total operative time was defined as the time taken from skin incision to completion of skin closure. At enrolment anthropometric data, smocking status, osteoarthritis stage according to Kellgren and Lawrence, Harris Hip Score, drugs assumption and comorbidities were recorded.

All the patients underwent serial blood tests, including complete blood count, PS and C-reactive protein (CRP) 24 h before arthroplasty and at 24, 48, 72 and 96 h postoperatively and at 3, 6 and 12-mo follow-up. The complication rate was recorded during the 12-mo follow-up.

### *Statistical analysis*

Statistical analysis was performed with SPSS v25.0 (SPSS Inc, Chicago, IL, United States). The Shapiro-Wilk Test was conducted. Pearson correlation test was performed to assess any relationship between non-modifiable risk factors and preoperative PS values at baseline.

Compared to the baseline, the paired t-student test was performed to assess PS and CRP modifications at 3, 6 and 12-mo follow-ups. *P* values below 0.05 were considered significant.

## RESULTS

A total of 96 patients (51 females; 45 males; mean age = 65.74 ± 5.58) were recruited in the present study. The main data of the study are summarized in Table 1.

Table 2 shows the correlation between non-modifiable risk factors and preoperative PS values at baseline; a significant correlation was observed between patients' age and preoperative PS levels. Notably, no correlation was found between preoperative creatinine and preoperative PS levels, since patients with chronic kidney disease were excluded from the present study.

Figure 1 shows the mean postoperative PS levels (Figure 1A) and the mean PS levels at 12-mo follow-ups (Figure 1B). The PS plasmatic concentration showed an increasing trend until 72 h post-op and started decreasing 96 h after surgery. During the 12-mo follow-up, the plasmatic PS concentration showed a significant increase at the three-month follow-up, when three patients out of 96 (3.125%) reported a soft-tissues infection. Higher levels (> 350 pg/mL) were recorded in these three patients at a 3-mo follow-up. No PJIs were diagnosed during the 12-mo follow-up.

Figure 2 shows plasmatic CRP kinetics after surgery (Figure 2A) and at 12-mo follow-up (Figure 2B). The plasmatic CRP curve still showed an increasing trend at 96 h after surgery. During the 12-mo follow-up, plasmatic CRP showed a reducing trend and it was not influenced by the presence of soft-tissue infections.

## DISCUSSION

PJIs are an emerging complication in prosthetic surgery, accounting for a relevant percentage of revision surgeries[27,28].

The pursuit of a biomarker able to improve the diagnosis and management of PJI, together with clinical findings and imaging modalities, is currently playing a central role in orthopaedics and traumatology[1].

Presepsin is an emerging biomarker studied in a wide range of infective conditions, including severe acute pancreatitis, neonatal sepsis, severe community-acquired pneumonia, pacemaker and ICD pocket infections, infections in patients with haematological malignancies, SSIs and PJIs. The present paper aims at depicting the normal postoperative plasmatic PS trend, in patients undergoing primary cementless THA, at 12-mo follow-up, to further depict a presepsin cut-off level for hip PJIs.

Our data showed PS has an increasing trend until 72 h post-op after THA surgery and starts decreasing 96 h after surgery. Furthermore, during the 12-mo follow-up, the plasmatic PS concentration showed a significant increase at the three-month follow-up, when three patients reported a soft-tissues infection. Hence, in the present study, plasmatic PS values are more sensitive to soft-tissues inflection, than CRP. Although the study sample is not so big and no cases of PJI have been observed in this trial, based on the study findings, the dosage of plasmatic PS concentration is recommended in patients undergoing THA before surgery, to exclude a concomitant unknown infection. However, future studies with a bigger sample size are needed to better define the limits of presepsin physiologic interval. The PS plasmatic concentration should be also assessed at 72 h after surgery, to assess the highest postoperative PS value, and at 96 h after surgery, when a decrease in plasmatic PS concentration is awaited. The lack of a plasmatic PS decrease, at 96 h after surgery could be a predictive factor of SSI or PJI.

These findings are consistent with the data reported by our research group in a preliminary report on perioperative presepsin levels in patients undergoing THA and TKA[25].

PS has been also studied in the assessment of PJIs by Marazzi *et al*[23], in a prospective multicentre study recruiting 100 patients who underwent revision surgery for aseptic loosening or PJI. These authors reported PS plasmatic levels were

**Table 1 Main data of the study**

| Characteristic | Values |
|---|---|
| Patients (*n*) | 96 |
| Gender, male, *n* (%) | 45 (46.875) |
| Age, mean ± SD | 65.74 ± 5.58 |
| Range | 54-77 |
| BMI (kg/m$^2$), mean ± SD | 26.34 ± 7.22 |
| Total operative time (min), mean ± SD | 86.54 ± 43.5 |
| Hospital staying (d), mean ± SD | 5.45 ± 1.76 |

**Table 2 Non-modifiable risk factors and presepsin values at recruitment: Pearson correlation test**

| | Presepsin | |
|---|---|---|
| | R | *P* value |
| Age | 0.74 | 0.018[a] |
| BMI (kg/m$^2$) | -0.259 | 0.734 |
| Gender | 0.19 | 0.44 |
| KLS | 0.287 | 0.16 |
| HHS | -0.17 | 0.645 |
| Creatinine | 0.056 | 0.852 |

[a]$P < 0.005$.
HHS: Harris Hip Score.

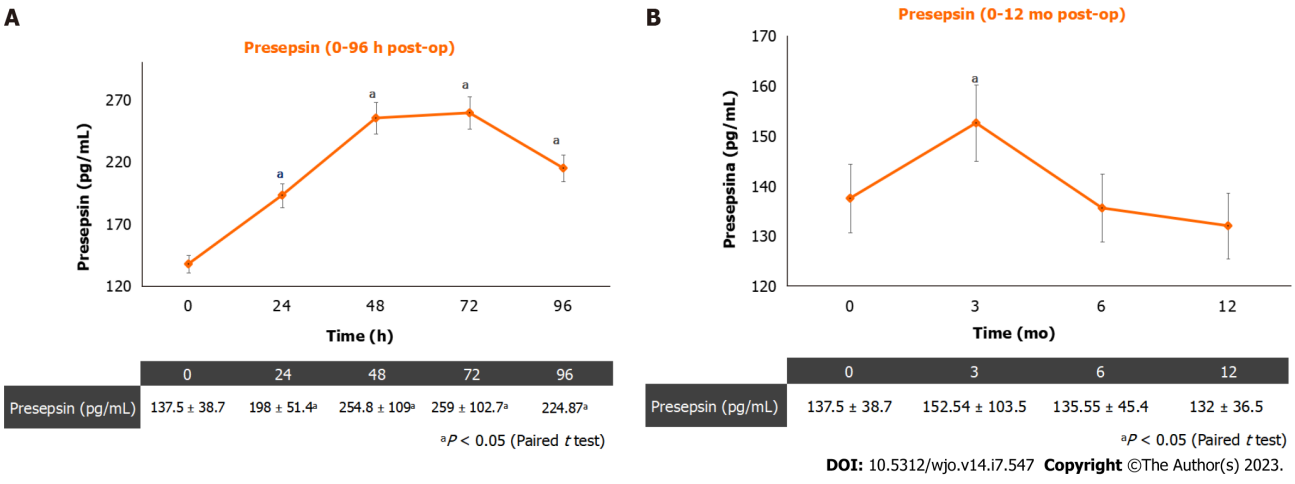


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**Figure 1 Presepsin levels.** A: Presepsin postoperative plasmatic concentration (0-96 h after surgery); B: Presepsin plasmatic levels during the 12-mo follow-up.

higher in the PJI group compared to the aseptic loosening group[23].

Koakutsu *et al*[30] have recently investigated the potential of PS in SSIs in a prospective observational study recruiting 118 patients who underwent elective major spine surgical procedures. These authors depicted an SSI in 3 patients out of 118; in these patients, higher levels (*i.e.*, > 300 pg/mL) were depicted in the first postoperative week[30].

Imagama *et al*[31] recently evaluated synovial fluid and serum PS, together with procalcitonin (PCT) serum levels, in 28 patients affected by osteoarthritis (OA), compared with 18 patients suffering from septic arthritis (SA). These authors observed that synovial fluid, plasmatic PS and plasmatic PCT were significantly higher in the SA group compared with the OA group[31]. Hence, Imagama *et al*[31] concluded that synovial fluid PS could be a useful biomarker to differentiate SA from OA.

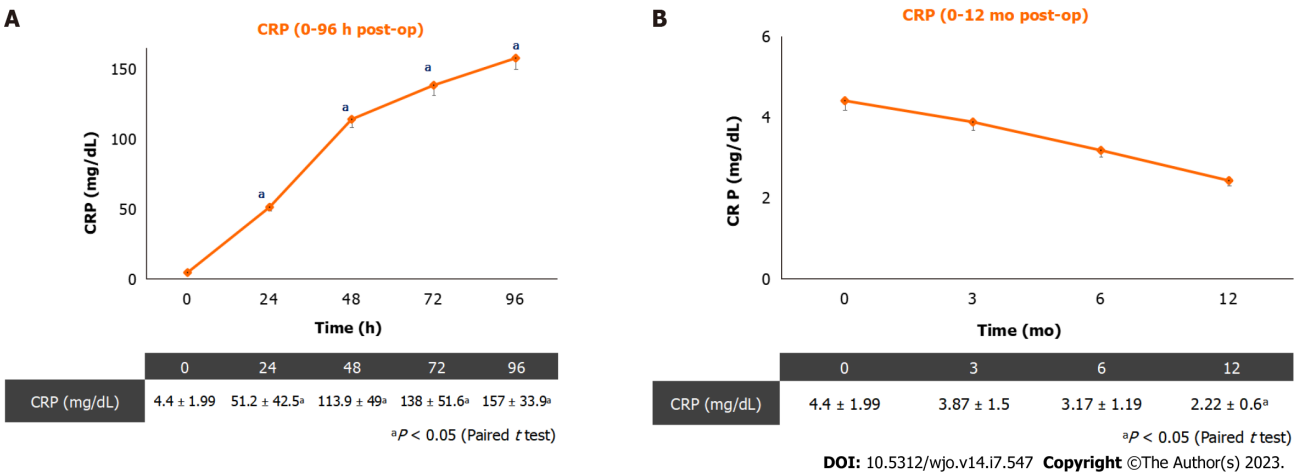


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**Figure 2 C-reactive protein levels.** A: C-reactive protein postoperative plasmatic concentration (0-96 h after surgery); B: C-reactive protein plasmatic levels during the 12-mo follow-up. CRP: C-reactive protein.

On the other hand, Busch *et al*[32], in a prospective cohort study on 53 patients with aseptic painful total shoulder, knee and hip arthroplasty and 27 patients affected by PJI, reported synovial fluid PS was not significantly higher in the PJI group, compared with the aseptic group. Synovial fluid presepsin specificity was 51% and sensitivity was 29%, with a cut-off value above 0.06 ng/mL[32].

Considering the above-mentioned findings, further studies with larger samples are awaited to better define the potential of serum and synovial PS concentration in the diagnosis of PJI.

The present study has some limitations. First of all, the sample size is not so large and no cases of PJI were recorded in the recruited patients during follow-up, hence the findings of the present study should be validated in a study with a larger sample size. Moreover, no control group was included in the present study and presepsin accuracy was not compared to other emerging biomarkers.

## CONCLUSION

The dosage of plasmatic PS concentration is highly recommended in patients undergoing THA, in the preoperative phase, to rule out any unknown infection.

The PS plasmatic concentration should be also assessed at 72 h after surgery, to assess the higher postoperative PS value, and at 96 h after surgery, when a PS decrease should be found. The lack of a presepsin decrease at 96 h after surgery might be a predictive factor of infection.

## ARTICLE HIGHLIGHTS

### *Research background*

Periprosthetic joint infections (PJIs) are a relevant cause of prosthetic surgery revision, accounting for 15% of failed total hip arthroplasties (THA).

### *Research Motivation*

Presepsin (PS) is released into the circulation following bacterial phagocytosis and the activation of other innate defence mechanisms. In a previous preliminary study, our research group defined the normal perioperative plasmatic levels of presepsin at 96 h postoperatively in 50 patients undergoing primary cementless THA and primary cemented total knee arthroplasties.

### *Research objectives*

This paper aims at depicting e normal postoperative PS plasmatic curve, in patients undergoing primary cementless THA, at 12-mo follow-up.

### *Research methods*

Patients undergoing primary THA were prospectively recruited. All the procedures were performed by the same anaesthesia and surgical équipe. The recruited patients underwent serial blood tests, including complete blood count, PS and C-reactive protein 24 h before arthroplasty and at 24, 48, 72 and 96 h postoperatively and at 3, 6 and 12-mo follow-up.

### *Research results*

Ninety-six patients (51 female; mean age = 65.74 years old) were included in the present study. The mean PS values were: 137.54 pg/mL before surgery, 192.08 pg/mL at 24 h post-op; 254.85 pg/mL at 48 h post-op; 259 pg/mL at 72 h post-op; 248.6 pg/mL at 96-h post-op; 140.52 pg/mL at 3-mo follow-up; 135.55 pg/mL at 6-mo follow-up and 130.11 pg/mL at 12-mo follow-up.

### *Research conclusions*

The assessment of plasmatic PS concentration is highly recommended in patients undergoing THA in the preoperative phase, to rule out any unknown infection. The PS plasmatic concentration should be also assessed at 72 h after surgery, to quantify the higher postoperative PS value, and at 96 h after surgery, when a decrease in PS should be found. The lack of a presepsin decrease at 96 h after surgery might predict a local infection.

### *Research perspectives*

Presepsin is an emerging biomarker in the diagnosis of PJIs. However, further studies with bigger samples are awaited to better define the role of serum and synovial PS in the diagnosis of PJI.

## FOOTNOTES

**Author contributions:** Bizzoca D, Moretti B and Solarino G designed the research study; Bizzoca D and Vicenti G performed the research; Bizzoca D wrote the manuscript; Moretti L and Piazzolla A revised the manuscript; all authors have read and approved the final manuscript.

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**Country/Territory of origin:** Italy

**ORCID number:** Davide Bizzoca 0000-0002-7516-2333; Andrea Piazzolla 0000-0003-2319-2108; Lorenzo Moretti 0000-0003-0106-6215; Giovanni Vicenti 0000-0002-7412-7990; Biagio Moretti 0000-0002-1234-8616; Giuseppe Solarino 0000-0001-6325-9691.

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