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Citation for final published version:

Sharouf, Feras , Hussain, Rahim N., Hettipathirannahelage, Sameera, Martin, John, Gray, William and Zaben, Malik 2020. C-reactive protein kinetics post elective cranial surgery. A prospective observational study. British Journal of Neurosurgery 34 (1) , pp. 46-50. 10.1080/02688697.2019.1680795

Publishers page: http://dx.doi.org/10.1080/02688697.2019.1680795

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C-reactive protein kinetics post elective cranial surgery. A prospective observational study

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ABSTRACT

Introduction: Post cranial surgery readmission, largely caused by surgical site infection (SSI), is a marker of patient-care quality requiring comprehensive discharge planning. Currently, discharge assessment is based on clinical recovery and basic laboratory tests, including C-reactive protein (CRP). Although CRP kinetics have been examined postoperatively in a handful of papers, the validity of CRP as a standalone test to predict SSI is yet to be explored.

Methods: A prospective observational study was performed on adult patients undergoing elective cranial surgery over a 3-month period. Laboratory data; CRP, white cell count (WCC), neutrophil cell count (NCC), and clinical data were assessed pre and post-operatively and were evaluated as predictors for safe discharge. Readmission rates within 1 month were recorded.

Results: In this study, 68 patients were included. About 8.6% were readmitted due to SSI. A postoperative peak in CRP was seen on day 2 with a value of 57 in the non-readmitted group, and 115 in the readmitted group. CRP dropped gradually to normal levels by day 5 in the non-readmitted group. A secondary CRP rise at day 5 was noted in the readmitted group with a sensitivity, specificity, and negative predictive value of 71%, 90%, and 96%, respectively. Interestingly, our ROC analysis indicates that a CRP value of less than 65 predicts safe discharge with a sensitivity of 86%, specificity of 89% and negative predictive value of 98% of safe discharge (area under the curve, AUC: 0.782). No significant difference in other inflammatory y markers was found between both groups.

Conclusions: CRP increases postoperatively for 4–5 d which could be a physiological response to surgery, however, prolonged elevation or a secondary increase in CRP may indicate an ongoing infection. Our data validate the potential use of CRP levels to predict SSI. A multicentre study is warranted to investigate the role of CRP in predicting SSI.

Introduction

Postoperative (post op) surgical site infection (SSI) is an important complication of cranial surgery with a reported incidence of 0.8–7%.[1,2] SSIs by definition occur within 30 d post-surgery and can be classified into scalp infection, bone flap osteomyelitis, subdural empyema, brain abscess, and/or meningitis.[3] Not only do SSIs negatively influence patients' clinical outcome, but also put a significant strain on hospital resources as they increase the likelihood of hospital readmission.[4] Readmission prevention has increasingly been used as a marker of patient care quality and requires comprehensive, safe discharge planning.[5]

The postoperative period after neurosurgery can be complicated by mild superficial wound infection and/or more serious infections that involve the bone, soft tissue, brain, or cerebrospinal fluid (CSF, meningitis). Neurosurgical patients often have ventricular drains, intracranial bolts, bladder, and intravenous catheters. These factors in combination with type and duration of surgery may increase the risks for developing infection.[1,2] The onset of SSI may be difficult to differentiate from other infections that exhibit similar symptoms. Postoperative changes may also be caused by opening of the dura and breakdown of blood products contributing to the clinical picture of fever, confusion, and meningism.[4] Confirmed diagnosis of bacterial meningitis can be made by detection of bacteria on Gram stain or isolation in culture, but CSF cultures remain negative in up to 70% of clinically suspected cases.[6] Currently, the assessment for safe discharge of postcranial surgery is based on a combination of clinical observations and the levels of serum inflammatory markers.[7]

Many biomarkers have been proposed to detect SSI including C-reactive protein (CRP). CRP is considered to be a sensitive systemic marker of inflammatory response.[8] However, despite its sensitivity, the usefulness of CRP for the detection of post op infection is limited by its non-specific increase after surgery.[9] After bacterial infection, CRP serum levels increase within 6 h.[8] However, CRP kinetics have rarely been investigated during the postoperative period. Therefore, we aimed in this prospective observational study to investigate the kinetics of CRP post-cranial surgery.

Methods

All adult patients who underwent elective cranial surgery at University Hospital of Wales (UHW) over a 3-month period from January 2016 to March 2016 were included in our study. The exclusion criteria for this study included patients less than 18 years of age, spinal surgery admissions, patients with other infections (such as urinary tract infections, chest infections, etc.), emergency surgery and trauma admissions, and lack of CRP results. The UHW neurosurgical and laboratory teams were blinded to our study.

Pre-operative and post op blood sample data were prospectively collected and assessed, including white cell count (WCC), neutrophil cell count (NCC), and CRP. Eighty-one patients underwent elective cranial surgery over the study period. Thirteen Patients were excluded as blood sample data were not available. The number of patients who had blood samples was as follows: 59 on day 0, 53 on day 1, 50 on day 2, 52 on day 3, 41 on day 4, 39 on day 5, 41 on day 6, and 38 on day 7.

Assessed clinical data included four-hourly recorded heart rate, blood pressure, respiratory rate, and body core temperature for subjects included in the study. Clinical data such as reason for admission and neurosurgical procedure were also recorded. The data were obtained from the patients' case notes, daily observation charts, and electronic records as soon as they were available. Patients were monitored daily for any ongoing, confirmed or suspected neurosurgical or other infections such as urinary tract infections and chest infections postoperatively until discharge. Patients attended with pre-op infections (chest or urine) were not included.

Electronic hospital records and admission register were daily monitored for readmissions. Only readmissions within 30 d postcranial surgery secondary to neurosurgical SSIs were counted to determine the readmission rate. The serum and clinical markers during the pre-operative and post op period were compared for readmitted and non-readmitted subgroups. The potential clinical and serum markers were then evaluated using receiver operating characteristic (ROC) curve analysis to determine their reliability as effective markers for safe discharge post-cranial surgery.

Data analysis was performed with Microsoft Excel 2016. Student t-test and linear regression tests were used for statistical analysis with a $p < .05$ considered significant. Continuous variables are presented as mean ± standard deviation (SD).

Results

Eighty-one patients underwent elective cranial surgery over the study period. Thirteen patients were excluded as CRP data was not available. The remaining 68 patients had 1:1 male to female ratio; with a mean age of 50 years (range 18–80).

Craniotomy for space-occupying lesion (SOL) was the commonest elective procedure with 38 cases, 5 patients had biopsy for SOL, 7 patients had pituitary surgery, 6 patients had CSF shunting, 5 patients had vascular surgery, and 7 other cases (as illustrated in Table 1). Seven patients (8.6%) were readmitted within 30 d of cranial surgery with SSI as illustrated in Figure 2. Notably, none of the excluded patients were readmitted during the follow up period (Table 1).

Data collected included body temperature and heart rate (as illustrated in Table 2).

Table 1. Neurosurgical procedures and readmission cases.

Procedure	Number of patients	Readmissions
SOL craniotomy	38 cases (55.8%)	5
SOL biopsy	5 cases (7.4%)	0
Pituitary surgery	7 cases (10.3%)	0
CSF shunting	6 cases (8.8%)	0
Vascular surgery	5 cases (7.4%)	0
Cranioplasty	3 cases (4.4%)	1
Temporal lobectomy	1 case (1.5%)	0
Trigeminal decompression	1 case (1.5%)	0
FMD	2 cases (2.9%)	1

Table 2. Values for mean body temperature and heart rate from D0 to D7.

Body temperature	Readmitted	Not-readmitted
Day 0	36.7	36.7
Day 1	36.8	36.8
Day 2	37	36.8
Day 3	37	36.9
Day 4	36.8	36.8
Day 5	36.8	36.7
Day 6	36.7	36.6
Day 7	36.6	36.7
Hear rate (HR)	Readmitted	Not-readmitted
Day 0	76	73
Day 1	80	77
Day 2	79	78
Day 3	79	77
Day 4	77	76
Day 5	78	76
Day 6	74	76
Day 7	75	76

Both WCC, as well as NCCs, increased on first postoperative day before it started to steadily decline back to normal levels with no secondary spikes during the first postoperative week (Figures 1 and 2). On postoperative day 2, WCC for not readmitted patients (ranged 5–24; median ¼ 9.7) was not different from, those for readmitted patients (5–20; median ¼ 11). p Value is .682 on day 2. Likewise, NCC on day 1 for not readmitted patients ranged from 4 to 3 with a median of 6.4, compared to 3–17 with a median of 8.4 for non-readmitted patients. p Value is .449 on day 2.

CRP kinetics was also recorded for all patients. Both groups had a primary CRP peak on day 2. Re-admitted group (secondary to infection), however, had a higher median CRP at 115mg/ L, compared to non-readmitted group (a median of 57 mg/L); (p<.001). Whilst CRP values for non-readmitted groups continued to fall and reached base line by postoperative day 4, readmitted group had a secondary rise of CRP value on day 5 (p<.001) (Figure 3). Secondary CRP rise on day 5, or failure to decrease as expected had sensitivity of 71%, specificity of 90%, and negative predictive value of 96% for detecting an early post op infection.

We evaluated cut-off points of CRP from tables of sensitivity and specificity. Using ROC curve analysis to determine CRP kinetics reliability as effective markers for safe discharge postcranial surgery, the optimal cut off point of CRP was less than 65 at post op day 2 for safe discharge. This is with sensitivity of 86%, specificity of 89%, and a negative predictive value of 98%. Our data has also demonstrated that an area under the curve (AUC) of 78% for detecting an early post op infection (Figure 4).

Body temperature and heart rate were evaluated over the first 7 d. No statistical difference was found between the readmitted and the non-readmitted group.

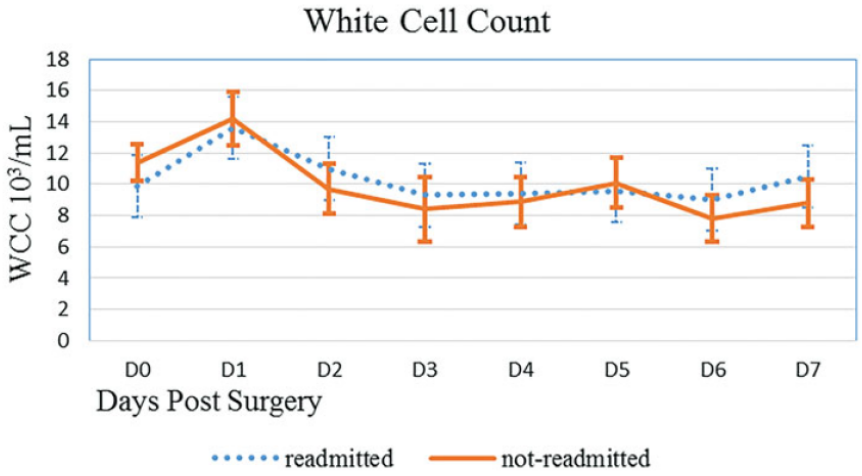

Figure 1. White cell count (WCC) kinetics on days 0–7.

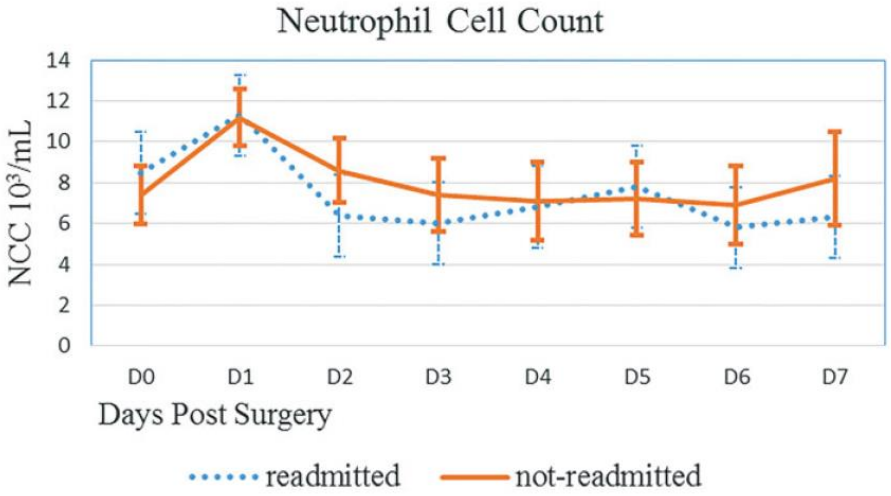

Figure 2. Neutrophil cell count (NCC) kinetics on days 0–7.

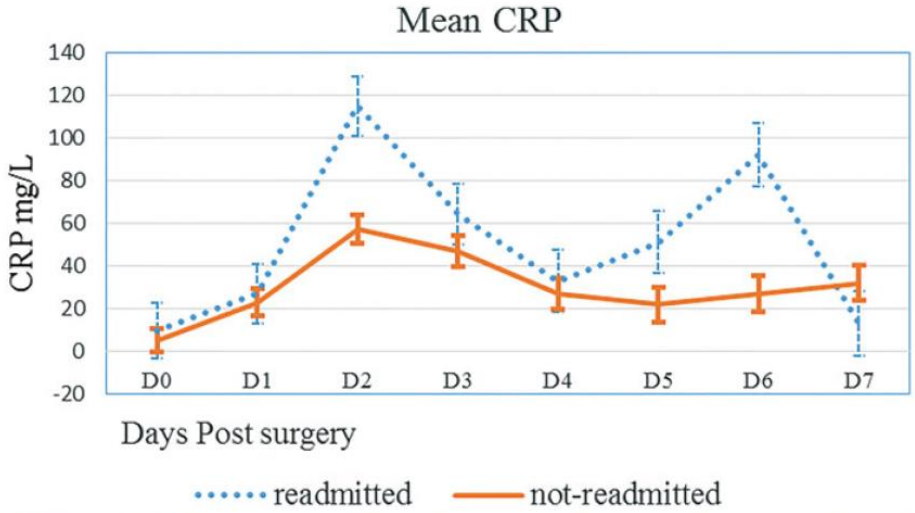

Figure 3. CRP kinetics on day 0 (D0) to day 7 (D7) in patients readmitted secondary to a SSI, and in patients who were not-readmitted.

Discussion

The aim of this study was to investigate CRP kinetics in patients after cranial surgery in an attempt to predict SSI. CRP is normally present in trace levels in serum but upsurges noticeably in response to a range of infectious and inflammatory stimuli including surgery and trauma.[10] In healthy individuals, a CRP level of less than 10 mg/L is considered normal.[11]

In our cohort, CRP levels prior to surgery were within the normal range (10 mg/L) for all patients included. Two different trends of CRP values were, however, observed after cranial surgery. One for the readmitted group secondary to infection, and the other for the non-readmitted group. For both groups of the study, CRP rapidly increased, reaching a peak on the second postoperative day (Figure 3). However, the median CRP value for the readmitted group was 115 mg/L, compared to 57 mg/L in the non-readmitted group (p<.001). For the non-readmitted group CRP values declined steadily and reached pre-operative levels on day 5.

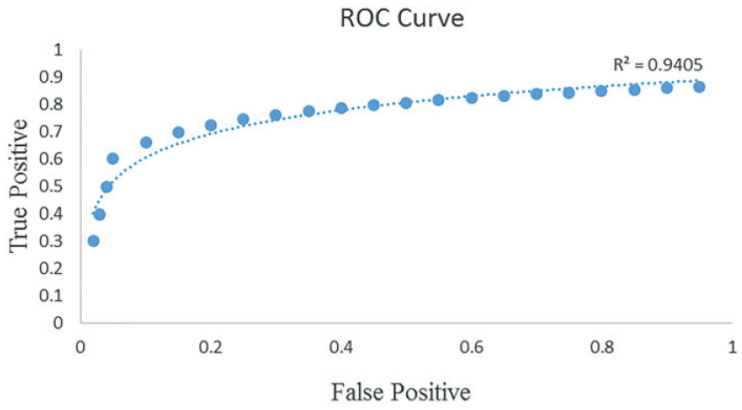

Figure 4. A cut off point of CRP < 65 at post op day 2 yielded sensitivity: 86%, specificity: 89%, and area under curve 78.2%.

In contrast, the readmitted group had a secondary rise in CRP values on day 5 (p<.001). A secondary peak in CRP is well documented in major abdominal surgery[12,13] and has been observed in other types of surgery, including spinal,[8,14] and intracranial surgery.[15] This secondary peak has been associated with increased risk of infection and other complications. Santonocito et al.[12] assessed post op CRP for neurosurgery, cardiac, vascular, thoracic, and abdominal surgery. They found that high CRP levels after day 4 of surgery, especially above 100 mg/L indicates the presence of postoperative infection.

Meyer et al.[16] assessed CRP progression in patients with post op infections after lumbar micro-discectomy. They found that CRP was a reliable screening test for early post op infection with a sensitivity, specificity, negative, and positive predictive values of 100%, 95.8%, 100%, and 48.4%, respectively.

In our cohort; secondary CRP rise on day 5, or failure to decrease as expected had sensitivity: 71%, specificity: 90%, and negative predictive value of 96% for detecting an early post op infection and readmission. CRP values did not correlate with age or sex and were similar in female and male patients.

WCC and NCC increased on the first postoperative day before it started to steadily decline back to normal levels with no secondary spikes during the first postoperative week. No differences in WCC and NCC were found between the readmitted ad the non-readmitted group.

Our findings were consistent with that of Al-Jabi and El- Shawarby (2010)[9] and Meyer et al. (1995).[16] Al-Jabi and El- Shawarby[9] assessed CRP progression in patients with post op infections after standard neurosurgical procedures. They found that a secondary CRP rise or failure to decrease as expected had sensitivity, specificity, negative, and positive predictive value of 100%, 93.1%, 100%, and 68.4%, respectively.

Current discharge risk-assessment screening models are based on clinical recovery as measured by regular clinical observations chart, and basic lab results including WCC and NCC. However, these conventional models can sometimes be misleading. In our cohort, there is virtually no difference in WCC, and NCC between both groups of the study (readmitted vs. non-readmitted) (Figures 1 and 2). SSIs account for a large proportion of postop discharge failure/readmission. The difficulty in assessing patients for SSIs lies in the common signs being confounded by the effects of the procedure itself, such as pain, fever, tachycardia, and raised WCC.

We evaluated cut-off points of CRP using ROC curve analysis. This is to determine CRP kinetics validity, as an effective marker for safe discharge post-cranial surgery. ROC curve is the plot that illustrates the connection between the sensitivity and (1- specificity) for every possible cut-off point for a diagnostic test. Total AUC is an index that measures the performance of the test. The larger the AUC, the better is the performance of the diagnostic test. The best cut-off is the combination of the highest true positive rate with the lowest false positive rate.[17] Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a single decision threshold.

The best diagnostic accuracy of postoperative CRP was obtained on day 2 with an AUC of 0.782 (Figure 4). A cut off point of CRP<65 mg/L at post op day 2 yielded sensitivity: 86% and specificity: 89%. Although a handful of papers have described CRP kinetics, this is the first prospective observational study in neurosurgery to robustly validate CRP as a predictor of SSI.

Increased CRP values during the first postoperative days do not necessarily indicate that an infection is ongoing, however, raised CRP > 65 mg/L is suggestive of early infection. An infection should also be considered with prolonged CRP elevation after the fourth postoperative day or when a second rise occurs.

Table 3 shows a summary of published post op CRP levels in variable surgeries, including neurosurgery, spinal, hip, and abdominal surgery. Looking at these different studies, a common theme of CRP kinetics emerges. Normal CRP levels prior to surgery are, usually, 5–10 mg/L. Peak CRP is observed around day 2 post surgery and CRP falls to pre-surgical levels around day 5. Infected or complicated cases, however, show a different pattern. CRP levels are much higher than non-infected cases on days 2 and 3. This is accompanied with sustained rise or a secondary peak on day 5. It is worth noting that the peak level varies according to type of surgery. The highest levels are found in abdominal surgery and lowest in neurosurgery. Understanding the determinants of peak level is essential, because values which are considerably higher than anticipated, may indicate a complication. Multiple studies identified a clear association between CRP levels and severity of intra-operative trauma,[21,22] duration of surgery,[8] and nature of the pathology.[9] Mirzayan et al.[9] found that CRP levels were significantly higher in intra-axial tumour resection compared with extra-axial tumours.[9] This difference could be due to surgical trauma and extent of surgery associated with intrinsic tumours. However, widespread variation in the concentrations of CRP in individual patients has been reported.[21]

Table 3. A summary of published post-operative CRP levels in variable surgeries, including neurosurgery, spinal, hip, and abdominal surgery.

CRP value after surgery	D0	D2	D3	D5
Intracranial (no infection) (Our cohort)	10	27	57	22
Intracranial (infection) (Our cohort)	5	23	115	51
Intracranial microsurgery[9]	5	32	22	10
Intracranial (no-infection)[8]	5	204	160	130
Intracranial (infection)[8]	10	194	175	188
Intracranial tumour surgery[15]	4	167	–	–
Neurosurgery (no infection)[12]	5	75	60	25
Neurosurgery (infection)[12]	10	150	150	175
Single-level PLIF[18]	4	127	–	60
Total hip replacement surgery[19]	10	150	110	50
Abdominal surgery-(uncomplicated)[20]	60	196	160	105
Abdominal surgery-(complicated)[20]	60	282	255	180

This variation in CRP may warrant the introduction of routine peri-operative CRP measurement, so it may be correlated against post op levels.

Our study is not without limitations. We have not studied the influence of operative time and level of trauma on CRP course. However, the main weakness of the study is the relatively small number of patients with post op infection and secondary readmission. These limitations can be overcome by conducting a national multicentre study investigating the role of CRP as a predictor of safe discharge.

Conclusion

CRP increases postoperatively for 4–5 d which could be a physiological response to surgery. However, prolonged elevation or a secondary increase in CRP may indicate an ongoing infection. CRP is more sensitive in the early postoperative period compared with WCC and NCC. Understanding the kinetics of CRP allows assessment of the degree of difference between actual and anticipated levels. We recommend that CRP is assessed in patients undergoing standard neurosurgical procedures pre and postoperatively and during the patients' hospital stay. We, however, do not advocate in-patient stay for prolonged periods of CRP follow up; general practitioners (GPs) in selected cases may be asked to do this test instead. A multicentre study may be warranted to further validate our findings.

Disclosure statement

The authors report no conflicts of interest.

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