Oral and Maxillofacial Surgery (2018) 22:129–134
https://doi.org/10.1007/s10006-018-0678-x

ORIGINAL ARTICLE

Behavior of C-reactive protein in association with surgery of facial fracture and the influence of dexamethasone

Johanna Snäll[1] · Jyrki Törnwall[1] · Anna Liisa Suominen[2,3] · Hanna Thorén[4,5]

Received: 15 August 2017 / Accepted: 9 January 2018 / Published online: 16 January 2018

Abstract

Purpose To clarify pre- and postoperative C-reactive protein (CRP) levels in patients with facial fractures and to investigate the influence of perioperatively administered dexamethasone on postoperative CRP levels.

Patients and methods Facial fracture patients were randomized to receive perioperatively a total dose of 30 mg of dexamethasone (Oradexon®), whereas patients in the control group received no glucocorticoid. The analysis included patients who had CRP measured pre- and postoperatively.

Results A total of 73 adult patients with facial fractures were included in the final analysis. Mean CRP level was elevated preoperatively and the level increased further after surgery. However, postoperative CRP rise was significantly impeded by dexamethasone ($p < 0.001$), regardless of gender, age, treatment delay, site of fracture, surgical approach, and duration of surgery. CRP rise halved on the 1st postoperative day when dexamethasone was used. In addition, dexamethasone resulted in a CRP decrease on the 2nd postoperative day, whereas the CRP rise continued in the control group.

Conclusions CRP rise is a normal body response after facial fracture and surgery that can be markedly reduced with dexamethasone. CRP changes should be considered with caution if perioperative dexamethasone is used.

Keywords Facial fracture · C-reactive protein · Dexamethasone · Glucocorticoids

Introduction

C-reactive protein (CRP) increases with inflammation and tissue damage [1]. CRP is primarily synthesized in the liver and produced in response to various stimuli mediators of the body, the most important of which are the inflammatory cytokines interleukin-6 (IL-6) and interleukin-1β (IL-1β) [2–4]. Therefore, CRP is applicable for measuring the body's response to inflammatory and infectious ailments.

Short-term glucocorticoids are beneficial for preventing nausea after general anesthesia [5]. In facial surgery, they prevent postoperative oedema [6] and diminish postoperative pain [6–8]. Glucocorticoids blunt the inflammatory and immune response of the body, affecting cytokine activity in various ways [9, 10]. As a negative consequence, however, surgical wound healing may be retarded, and the risk for surgical site infection may increase [11–13]. The postoperative increase in CRP may be attenuated by glucocorticoids [14, 15]. How and to what extent perioperatively administered glucocorticoids affect postoperative CRP levels after surgery of facial fractures in particular remain unknown.

The aims of the study were to clarify (1) pre- and postoperative CRP levels in patients diagnosed with and undergoing surgical intervention of facial fracture and (2) how and to what extent perioperatively administered high-dose, short-term dexamethasone influences postoperative CRP levels.

✉ Johanna Snäll
johanna.snall@helsinki.fi

1 Department of Oral and Maxillofacial Diseases, University of Helsinki and Helsinki University Hospital, FI-00029 Helsinki, Finland

2 University of Eastern Finland, Institute of Dentistry, Kuopio, Finland

3 Department of Oral and Maxillofacial Surgery, Kuopio University Hospital, Kuopio, Finland

4 Department of Oral and Maxillofacial Surgery, Institute of Dentistry, University of Turku, Turku, Finland

5 Department of Oral and Maxillofacial Diseases, Turku University Hospital, Turku, Finland

Patients and methods

Study design

The patients in this study were drawn from a larger cohort of healthy adult dentate patients who had been recruited for a clinical follow-up study in order to clarify the benefits and drawbacks of perioperative dexamethasone in association with surgery of facial fracture. Included in the follow-up study were patients with three types of simple fractures: (1) mandibular fractures (i.e., one or two fractures in dentate areas that had been treated with open reduction and fixed with titanium miniplates in one or two intraoral approaches), (2) zygomatic complex fractures (i.e., unilateral fractures that had been treated with open or closed reduction with or without fixation with titanium miniplates via an intra- and/or extraoral approach), and (3) orbital wall fractures (i.e., fractures that had been reconstructed with titanium mesh or a bone transplant from the iliac crest).

For each fracture type, the patients were randomly assigned either to serve as a control, receiving no glucocorticoids, or to receive dexamethasone (Oradexon®) to a total dose of 30 mg. Randomization was implemented by sealed envelopes. The patients in the study group were given dexamethasone 10 mg intravenously during induction of anesthesia and an additional 10 mg intramuscularly every 8 h for 16 h, for a total dose of 30 mg. All patients were given antibiotics until the 7th to 10th postoperative day, starting with three doses of cefuroxime 1.5 g intravenously in the ward during the first 24 h postoperatively and followed by three doses of cephalexin 500 mg orally per day. Patients with allergies were given four doses of clindamycin per day by corresponding routes. No surgical drains were used.

Inclusion and exclusion criteria for the analysis

Of 130 potential patients fulfilling the inclusion criteria, 122 agreed to participate in the follow-up study. Of these, 49 were excluded from the analysis because of missing preoperative or first postoperative day CRP values, failure to receive all scheduled dexamethasone doses, or postoperative surgical site infection. Thus, a total of 73 patients were included in this study.

Evaluation of CRP levels

Measurements of CRP levels were not included in the initial study protocol. For the present analysis, CRP values were identified retrospectively from the patient files.

CRP was measured using an immunoturbometric assay (Roche Tina-Quant C-Reactive Protein CRPL3 Gen. 3; Roche, Basel, Switzerland) and expressed as mg/L. The normal value is < 3 mg/L. From the laboratory reports, preoperative CRP levels as well as the levels on the 1st and 2nd postoperative days were recorded. All preoperative CRP measurements were performed 0–1 day before surgery and before dexamethasone administration.

Study variables

The outcome variable was CRP. The primary predictor variable was the perioperative use of dexamethasone. Other explanatory variables included in the analysis were age, gender, treatment delay, fracture type, surgical approach, and duration of surgery.

Data analysis

For data analysis, age of the patients was classified as (1) < 37 years or (2) ≥ 37 years. Treatment delay was classified as (1) < 2 days, (2) ≥ 2 but < 5 days, and (3) ≥ 5 days. Surgical approach was classified as (1) extraoral (including patients who underwent exclusively extraoral approach) and (2) intraoral (including patients who underwent exclusively intraoral or combined intra- and extraoral approach). Duration of surgery was classified as (1) < 45 min or (2) ≥ 45 min.

Significant differences of gender, fracture site, and surgical approach with perioperative use of dexamethasone were evaluated by Chi-square tests. Differences in means of age, duration of surgery, preoperative level of CRP, and change of CRP from preoperative level to 1st and 2nd postoperative day according to perioperative use of dexamethasone were analyzed with Wilcoxon two-sample test. Differences in means of CRP from preoperative level to 1st and 2nd postoperative day according to perioperative use of dexamethasone were also analyzed as stratified by gender, age group, treatment delay, fracture site, surgical approach, and duration of surgery.

Results

Table 1 shows demographic and clinical data of the 73 patients. Dexamethasone was administered to 37 (51%) of the 73 patients. All 73 patients had CRP values measured preoperatively and on the 1st postoperative day. Sixty-five patients had an additional CRP value measured on the 2nd postoperative day. When patients who received dexamethasone were compared with those who did not receive it, no significant differences were observed in male/female ratio, average age, average treatment delay, fracture site (mandibular, zygomatic complex, or orbital fractures), surgical approach, average duration of surgery, and average level of CRP preoperatively.

The mean preoperative CRP level in 73 patients was elevated to 11.2 mg/L (Table 1). Mean CRP value increased

Table 1 Demographic and clinical data of 73 patients with facial fractures

Variable	All patients ($n = 73$)	DX+ ($n = 37$)	DX− ($n = 36$)	p value DX+ vs. DX−
Measured CRP levels (no. of patients)				
Preoperatively	73	37	36	NS
1st postoperative day	73	37	36	NS
2nd postoperative day	65	33	32	NS
Gender (no. of patients)				
Male/female	58/15	30/7	28/8	NS
Age (years)				
Range	18–71	18–82	20–71	
Average	38	37	39	NS
Treatment delay (days)				
Range	0–19	0–11	0–19	
Average	4	4	4	NS
Fracture site (no. of patients)				
Mandible	29	16	13	NS
Zygomatic complex	29	14	15	NS
Orbit	15	7	8	NS
Surgical approach (no. of patients)				
Intraoral/extraoral	44/29	23/14	21/15	NS
Duration of surgery (min)				
Range	8–128	8–140	21–128	
Average	52.4	51	54	NS
Preoperative CRP level (mg/L)				
Range	2–32	2–91	2–57	
Average	11.1	12.9	9.3	NS

DX+ patients who received dexamethasone, *DX−* patients who did not receive dexamethasone

further after surgery in both the dexamethasone group and controls. However, dexamethasone impeded postoperative CRP rise significantly (Table 2). The mean CRP value increased by 28.3 units in the controls, but by only 5.1 units in the dexamethasone group during the first postoperative day ($p < 0.001$). On the second postoperative day, the mean CRP value increased further in the controls, whereas it decreased in the dexamethasone group ($p < 0.001$).

Table 3 summarizes the changes in mean CRP levels according to use of dexamethasone stratified by explanatory variables (gender, age group, treatment delay, site of fracture, surgical approach, or duration of surgery). Dexamethasone impeded postoperative CRP rise, the findings being statistically significant in each strata, except on the first postoperative day in females and in patients whose treatment delay was < 2 days.

Discussion

The aims of this study were to clarify (1) pre- and postoperative CRP levels in patients diagnosed with and

Table 2 Association between changes in mean CRP levels and dexamethasone use in 73 patients with facial fractures

Mean CRP (mg/L)	DX+		DX−		
	Mean CRP (mg/L)	Difference from preoperative	Mean CRP (mg/L)	Difference from preoperative	DX+ vs. DX−
Preoperatively	12.9		9.3		
1st postoperative day	18.0	5.1	37.6	28.3	$p < 0.001$
2nd postoperative day	8.6	−4.3	45.6	36.3	$p < 0.001$

DX+ patients who received dexamethasone, *DX−* patients who did not receive dexamethasone

Table 3 Association between changes in mean CRP levels and predictors

Predictor	DX+ ($n = 37$)		DX− ($n = 36$)		
	Mean CRP (mg/L)	Difference from preoperative	Mean CRP (mg/L)	Difference from preoperative	p value DX+ vs. DX−
Males ($n = 58$)					
Preoperatively	15.4		10.4		
1st postoperative day	21.5	6.1	45.2	34.8	$p < 0.001$
2nd postoperative day	10.0	− 5.4	55.0	44.6	$p < 0.001$
Females ($n = 15$)					
Preoperatively	2.0		5.4		
1st postoperative day	2.6	0.6	11.0	5.6	$p = 0.058$
2nd postoperative day	2.0	0.0	12.0	6.6	$p = 0.018$
Age ≤ 37 years ($n = 37$)					
Preoperatively	20.3		7.9		
1st postoperative day	27.4	7.1	52.6	44.7	$p = 0.005$
2nd postoperative day	12.1	− 8.2	68.9	61.0	$p = 0.004$
Age ≥ 37 years ($n = 36$)					
Preoperatively	3.2		10.4		
1st postoperative day	5.6	2.4	25.7	15.3	$p = 0.001$
2nd postoperative day	3.2	0.0	27.5	17.1	$p < 0.001$
Treatment delay < 2 days ($n = 19$)					
Preoperatively	9.1		8.4		
1st postoperative day	30.8	21.6	53.8	45.5	$p = 0.215$
2nd postoperative day	14.4	5.3	66.6	58.3	$p = 0.030$
Treatment delay ≥ 2 < 5 days ($n = 27$)					
Preoperatively	25.8		11.6		
1st postoperative day	24.0	− 1.8	34.3	22.7	$p = 0.005$
2nd postoperative day	10.7	− 15.1	37.7	26.1	$p = 0.001$
Treatment delay ≥ 5 days ($n = 27$)					
Preoperatively	2.9		7.6		
1st postoperative day	5.5	2.6	26.3	18.8	$p = 0.005$
2nd postoperative day	3.3	0.4	31.8	24.2	$p = 0.002$
Mandibular fracture ($n = 29$)					
Preoperatively	25.9		15.2		
1st postoperative day	35.4	9.6	68.4	53.2	$p = 0.003$
2nd postoperative day	15.7	−10.2	72.7	57.5	$p = 0.001$
Zygomatic complex fracture ($n = 29$)					
Preoperatively	2.9		6.1		
1st postoperative day	5.4	2.5	22.5	16.4	$p = 0.007$
2nd postoperative day	2.9	0.0	33.8	27.6	$p = 0.001$
Orbital fracture ($n = 15$)					
Preoperatively	3.1		5.5		
1st postoperative day	3.0	− 0.1	15.9	10.4	$p = 0.004$
2nd postoperative day	2.2	− 1.0	12.7	7.2	$p = 0.010$
Intraoral approach ($n = 44$)					
Preoperatively	18.7		12.2		
1st postoperative day	27.0	8.3	53.5	41.3	$p = 0.001$
2nd postoperative day	12.3	− 6.4	61.1	48.9	$p < 0.001$
Extraoral approach ($n = 29$)					
Preoperatively	3.3		5.1		

Table 3 (continued)

Predictor	DX+ ($n = 37$)		DX− ($n = 36$)		
	Mean CRP (mg/L)	Difference from preoperative	Mean CRP (mg/L)	Difference from preoperative	p value DX+ vs. DX−
1st postoperative day	3.1	− 0.2	15.4	10.3	$p < 0.001$
2nd postoperative day	2.1	− 1.2	16.0	10.9	$p < 0.001$
Duration of surgery < 45 min ($n = 36$)					
Preoperatively	12.5		9.3		
1st postoperative day	16.7	4.3	20.3	10.9	$p = 0.049$
2nd postoperative day	8.5	− 4.0	21.9	12.6	$p = 0.010$
Duration of surgery ≥ 45 min ($n = 37$)					
Preoperatively	13.4		9.3		
1st postoperative day	19.4	6.0	51.5	42.3	$p < 0.001$
2nd postoperative day	8.7	− 4.7	64.1	54.8	$p < 0.001$

DX+ patients who received dexamethasone, *DX−* patients who did not receive dexamethasone

undergoing surgical intervention of facial fracture and (2) how and to what extent perioperatively administered high-dose, short-term dexamethasone influences postoperative CRP levels.

Our results revealed an elevated mean CRP level of 11.2 mg/L preoperatively. The level increased further after surgery in both the dexamethasone group and controls. However, postoperative CRP rise was significantly impeded by dexamethasone, regardless of gender, age, treatment delay, site of fracture, surgical approach, and duration of surgery.

Regarding the relationship between CRP level and facial trauma, our results are in line with those of Iizuka et al. [16]. The authors had shown an association between mandibular fracture and increase in CRP value preoperatively. Further, they had observed that after surgery there was always an increase in CRP level, which reached its maximum on the second postoperative day. Parallel results were reported by Kiran and Desai, who observed a marked increase in CRP levels during the first postoperative 24 h in patients treated for mandibular fractures, the levels normalizing about 1 week after surgery [17].

Previous papers have demonstrated the benefits of systemic dexamethasone in association with recovery from surgery in general [14] and from facial surgery in particular [8, 18]. Dexamethasone is also preferred as an antiemetic drug [19]; however, our recent study showed no benefit in routine use in facial trauma patients [20]. As dexamethasone impedes inflammatory response in general and CRP rise in particular, diagnosis and treatment of postoperative surgical site infection may be delayed. This is important to acknowledge since dexamethasone itself may predispose to infection, which we have shown in previous facial fracture studies [11–13]. The same phenomenon was also shown by Abdelmalak et al. who observed a higher rate of infections in vascular surgery patients with perioperatively administered dexamethasone, despite significantly decreased CRP levels [15]. We consider the use of dexamethasone in association with surgical treatment of facial fracture to be beneficial in selected patients. For the unexperienced surgeon, it is useful to be aware of the association between facial trauma, facial surgery, and CRP increase in order to avoid unnecessary infection diagnoses. However, the interpretation of CRP becomes more complicated if dexamethasone is used, as shown here.

One drawback of this study was that a considerable portion of the patients was excluded due to missing CRP variables. Preoperative CRP measurements were not included in the primary study protocol, and the variables were therefore collected retrospectively. On the other hand, the findings are undeniable and consistent in all fracture groups, and confounding factors, such as multiple fractures and infections, were not included. It should be noted that also other trauma-related factors, such as multiple injuries or massive soft tissue injuries, may affect CRP changes.

The clinical relevance of CRP and its function as an inflammation mediator are somewhat unclear. CRP has several functions in the periphery. In damaged tissues, it is an essential protein that activates the complement cascade on the surface of necrotic cells [21]. It also accelerates pro-migratory functions in wounds, supports the activity of monocytes [22], and promotes angiogenesis [23]. Recent studies have revealed the biological role of CRP to be more complex than previously thought. Future research should elucidate the clinical effects of pharmacological systemic CRP. However, CRP measurements are not

reliable indicators of inflammation or infection in patients on perioperative glucocorticoid therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval The study protocol was approved by the Ethics Committee of the Department of Surgery and the Internal Review Board of the Division of Musculoskeletal Surgery, Helsinki University Hospital, Finland (Dno 33/E6/06). Informed consent was obtained from all participants.

All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

References

1. Pepys MB (1981) C-reactive protein fifty years on. Lancet 1(8221): 653–657
2. Majello B, Arcone R, Toniatti C, Ciliberto G (1990) Constitutive and IL-6-induced nuclear factors that interact with the human C-reactive protein promoter. EMBO J 9(2):457–465
3. Radtke S, Wuller S, Yang XP, Lippok BE, Mutze B, Mais C, de Leur HS, Bode JG, Gaestel M, Heinrich PC, Behrmann I, Schaper F, Hermanns HM (2010) Cross-regulation of cytokine signalling: pro-inflammatory cytokines restrict IL-6 signalling through receptor internalisation and degradation. J Cell Sci 123(6):947–959. https://doi.org/10.1242/jcs.065326
4. Kleemann R, Gervois PP, Verschuren L, Staels B, Princen HM, Kooistra T (2003) Fibrates down-regulate IL-1-stimulated C-reactive protein gene expression in hepatocytes by reducing nuclear p50-NFkappa B-C/EBP-beta complex formation. Blood 101(2): 545–551. https://doi.org/10.1182/blood-2002-06-1762
5. Hirayama T, Ishii F, Yago K, Ogata H (2001) Evaluation of the effective drugs for the prevention of nausea and vomiting induced by morphine used for postoperative pain: a quantitative systematic review. Yakugaku Zasshi 121(2):179–185. https://doi.org/10.1248/yakushi.121.179
6. Dan AE, Thygesen TH, Pinholt EM (2010) Corticosteroid administration in oral and orthognathic surgery: a systematic review of the literature and meta-analysis. J Oral Maxillofac Surg 68(9):2207–2220. https://doi.org/10.1016/j.joms.2010.04.019
7. Markiewicz MR, Brady MF, Ding EL, Dodson TB (2008) Corticosteroids reduce postoperative morbidity after third molar surgery: a systematic review and meta-analysis. J Oral Maxillofac Surg 66(9):1881–1894. https://doi.org/10.1016/j.joms.2008.04.022
8. Kormi E, Snall J, Koivusalo AM, Suominen AL, Thoren H, Tornwall J (2017) Analgesic effect of perioperative systemic dexamethasone on blowout fracture surgery. J Oral Maxillofac Surg 75(6):1232–1237. https://doi.org/10.1016/j.joms.2016.09.026
9. Gadek-Michalska A, Tadeusz J, Rachwalska P, Bugajski J (2013) Cytokines, prostaglandins and nitric oxide in the regulation of stress-response systems. Pharmacol Rep 65(6):1655–1662. https://doi.org/10.1016/S1734-1140(13)71527-5
10. Zen M, Canova M, Campana C, Bettio S, Nalotto L, Rampudda M, Ramonda R, Iaccarino L, Doria A (2011) The kaleidoscope of glucorticoid effects on immune system. Autoimmun Rev 10:305–310
11. Snall J, Apajalahti S, Suominen AL, Tornwall J, Thoren H (2015) Influence of perioperative dexamethasone on delayed union in mandibular fractures: a clinical and radiological study. Med Oral Patol Oral Cir Bucal 20:e621–e626
12. Snall J, Kormi E, Koivusalo AM, Lindqvist C, Suominen AL, Tornwall J, Thoren H (2014) Effects of perioperatively administered dexamethasone on surgical wound healing in patients undergoing surgery for zygomatic fracture: a prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol 117:685–689
13. Thoren H, Snall J, Kormi E, Numminen L, Fah R, Iizuka T, Lindqvist C, Tornwall J (2009) Does perioperative glucocorticosteroid treatment correlate with disturbance in surgical wound healing after treatment of facial fractures? A retrospective study. J Oral Maxillofac Surg 67(9):1884–1888. https://doi.org/10.1016/j.joms.2009.04.089
14. Bisgaard T, Klarskov B, Kehlet H, Rosenberg J (2003) Preoperative dexamethasone improves surgical outcome after laparoscopic cholecystectomy: a randomized double-blind placebo-controlled trial. Ann Surg 238(5):651–660. https://doi.org/10.1097/01.sla.0000094390.82352.cb
15. Abdelmalak BB, Bonilla A, Mascha EJ, Maheshwari A, Tang WH, You J, Ramachandran M, Kirkova Y, Clair D, Walsh RM, Kurz A, Sessler DI (2013) Dexamethasone, light anaesthesia, and tight glucose control (DeLiT) randomized controlled trial. Br J Anaesth 111(2):209–221. https://doi.org/10.1093/bja/aet050
16. Iizuka T, Lindqvist C (1991) Changes in C-reactive protein associated with surgical treatment of mandibular fractures. J Oral Maxillofac Surg 49(5):464–467. https://doi.org/10.1016/0278-2391(91)90168-L
17. Kiran DN, Desai R (2012) Estimation of C-reactive protein associated with mandibular fracture. J Maxillofac Oral Surg 11(1):67–71. https://doi.org/10.1007/s12663-011-0278-x
18. Flood TR, McManners J, el-Attar A, Moos KF (1999) Randomized prospective study of the influence of steroids on postoperative eye-opening after exploration of the orbital floor. Br J Oral Maxillofac Surg 37(4):312–315. https://doi.org/10.1054/bjom.1999.0024
19. De Oliveira GS, Castro-Alves LJ Jr, Ahmad S, Kendall MC, McCarthy RJ (2013) Dexamethasone to prevent postoperative nausea and vomiting: an updated meta-analysis of randomized controlled trials. Anesth Analg 116(1):58–74. https://doi.org/10.1213/ANE.0b013e31826f0a0a
20. Haapanen A, Thoren H, Tornwall J, Suominen AL, Snall J (2017) Postoperative nausea and vomiting in facial fracture patients: a randomized and controlled trial on the effect of dexamethasone. Int J Oral Maxillofac Surg 46(10):1267–1270. https://doi.org/10.1016/j.ijom.2017.03.026
21. Mihlan M, Blom AM, Kupreishvili K, Lauer N, Stelzner K, Bergstrom F, Niessen HW, Zipfel PF (2011) Monomeric C-reactive protein modulates classic complement activation on necrotic cells. FASEB J 25(12):4198–4210. https://doi.org/10.1096/fj.11-186460
22. Braig D, Kaiser B, Thiele JR, Bannasch H, Peter K, Stark GB, Koch HG, Eisenhardt SU (2014) A conformational change of C-reactive protein in burn wounds unmasks its proinflammatory properties. Int Immunol 26(8):467–478. https://doi.org/10.1093/intimm/dxu056
23. Bello G, Cailotto F, Hanriot D, Kolopp-Sarda MN, Latger-Cannard V, Hess K, Zannad F, Longrois D, Ropars A (2008) C-reactive protein (CRP) increases VEGF-A expression in monocytic cells via a PI3-kinase and ERK 1/2 signaling dependent pathway. Atherosclerosis 200(2):286–293. https://doi.org/10.1016/j.atherosclerosis.2007.12.046