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Preoperative High-Dose Corticosteroids in Digestive Cancer Surgery
A Randomized Clinical Trial

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IMPORTANCE Modulating perioperative inflammation could be associated with fewer postoperative complications and better outcomes in major digestive surgery. The clinical benefit of corticosteroids with this purpose remains controversial.

OBJECTIVE To assess whether preoperative high-dose corticosteroids improve postoperative outcomes after surgery for digestive cancer.

DESIGN, SETTING, AND PARTICIPANTS This double-blind, placebo-controlled, superiority randomized clinical trial included patients undergoing elective surgery with curative intent for digestive cancer. This was a multicenter trial with the participation of 23 French hospitals working as a reference for digestive surgical oncology. Among patients referred for major digestive surgery to the participating centers, those undergoing surgery for digestive cancer with a curative intent between 2019 and 2023 were randomized. Patients undergoing only hepatic surgery without digestive anastomosis were excluded.

INTERVENTIONS Patients included were randomized to receive either 20 mg/kg of intravenous methylprednisolone at the time of anesthesia or a placebo with an identical aspect.

MAIN OUTCOMES AND MEASURES The primary end point was the onset of major postoperative complications within 30 days after surgery. Secondary end points were postoperative infections, intra-abdominal infections, wound infections, unsatisfactory wound healing within 30 days after surgery, and the length of hospital stay after surgery.

RESULTS Among 2461 patients referred for major digestive surgery, 1210 patients (mean [SD] age, 65.9 [11.3] years; 762 male [63%]) undergoing surgery for digestive cancer were randomized. Among the 1188 patients with follow-up at postoperative day 30 (594 per arm), major postoperative complications did not significantly differ between the 2 groups (139 of 594 [23%] receiving methylprednisolone vs 119 of 594 [20%] receiving placebo; $P = .16$). Secondary outcomes did not differ either between the group receiving methylprednisolone and the group receiving placebo (postoperative infections: 182 of 594 [31%] vs 177 of 594 [30%]; $P = .75$; intra-abdominal infections: 142 of 594 [24%] vs 126 of 594 [21%]; $P = .27$; unsatisfactory wound healing: 87 of 594 [15%] vs 69 of 594 [12%]; $P = .13$; mean [SD] length of hospital stay: 13.21 [8.59] days vs 12.97 [8.1] days; $P = .93$).

CONCLUSIONS AND RELEVANCE A preoperative pulse dose of corticosteroids had no benefit on postoperative outcomes in elective digestive cancer surgery and should not be recommended in routine practice.

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Visual Abstract
Invited Commentary
Supplemental content

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Surgery is a tissue aggression that leads to a physiological inflammatory response. In patients with cancer undergoing surgery, this physiological response adds to the effects of the disease itself. Potential postoperative complications can further increase the inflammatory response.

It has been shown that intense perioperative inflammation has a negative influence on postoperative morbidity (particularly surgical infection), recovery, and length of hospital stay.[1,2] Perioperative inflammation can also impair the immune response to surgical site infections and has a negative impact on cancer-related outcomes, whether complications occur or not.[3-8] Therefore, modulating perioperative inflammation to reduce the incidence of severe complications could potentially improve outcomes after cancer surgery.[8,9]

Several therapies have been developed to this effect and implemented in the perioperative period. Immunonutrition, for instance, has a proven anti-inflammatory effect and decreases the onset of postoperative infections.[10] Postsurgical enhanced recovery programs may also have such an effect.[8,9] Regarding the use of medications, nonsteroidal anti-inflammatory drugs have an anti-inflammatory effect, but their safety in digestive surgery remains a concern.[11] In recent years, several trials have assessed the benefit of a single pulse dose of perioperative corticosteroids in different fields of surgery, both elective and unplanned, in terms of postoperative complications, length of stay (LOS), pain, nausea and vomiting, neurocognitive dysfunction, and systemic inflammatory response. Although the safety of perioperative corticosteroids has been established, the benefits beyond the prevention of postoperative nausea and vomiting are not clear.[12-14] Most trials found an effective decrease in inflammatory markers, but the clinical benefit remains controversial, except in hepatic surgery where the benefit seems established. Previous trials conducted in digestive surgery included a small number of patients, frequently including benign and malignant disease, and did not evaluate meaningful clinical end points. The administered drugs and their doses also varied considerably, ranging from 8 mg of dexamethasone to doses as high as 30 mg per kilogram of body weight of methylprednisolone.[12] In cancer surgery, the specific effect of perioperative corticosteroids has not been assessed in relation to postoperative complications nor in terms of cancer outcomes.

The Benefit of a Flash Dose of Corticosteroids in Digestive Surgical Oncology: a Randomized, Double-Blind, Placebo-Controlled Trial (CORTIFRENCH) is a multicenter trial aiming to assess the benefit of a preoperative pulse dose of methylprednisolone to prevent postoperative complications and to improve recovery after surgery for digestive cancer.

Key Points

Question Could a single preoperative high dose of corticosteroids decrease morbidity and improve postoperative recovery in digestive cancer surgery?

Findings This multicenter, double-blind, placebo-controlled, randomized clinical trial including 1210 adults did not find any significant benefit of a preoperative pulse dose of corticosteroids in the prevention of severe complications or in recovery after surgery for digestive cancer.

Meaning Study results show that a flash dose of corticosteroids had no benefit on postoperative outcomes in elective digestive cancer surgery and should not become part of routine practice.

Methods

Study Design

The CORTIFRENCH trial is a multicenter, phase 3 superiority trial conducted in 23 French university and nonuniversity hospitals to assess whether a preoperative pulse dose of corticosteroids reduces major morbidity after surgery for digestive cancer. The secondary objectives were to assess the safety of a preoperative pulse dose of corticosteroids and their effect on postoperative and intra-abdominal infections at postoperative day 30 (POD 30), hospital LOS, and 3-year overall and disease-free survival. The protocol was approved by an independent ethics committee and the French National Agency for the Safety of Medicines and Health Products according to French and European regulations, and was registered at ClinicalTrials.gov and on the Clinical Trials Information System after the implementation of the European Union regulation. A previous safety trial was conducted in colorectal surgery following the request of the Fédération de Recherche en Chirurgie (FRENCH) research network.[14] The study protocol of CORTIFRENCH has been published elsewhere (Supplement 1).[2] Inclusions started in July 2019 but were interrupted in 2020 due to the COVID-19 pandemic. The last patient was included in December 2023. The present study reports the results of the primary end point of the trial and the secondary end points evaluable at POD30. All participants provided written informed consent. This study followed the 2025 Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.[15]

Population

Inclusion criteria were adults undergoing elective surgery with curative intent for digestive cancer (except primary liver cancer), affiliated with the French National Health System. Participant race and ethnicity data were not gathered as they were not of interest in this study.

The exclusion criteria included surgery in an emergency or palliative setting, surgery limited to liver resection, surgery with concomitant hyperthermic intraperitoneal chemotherapy, American Society of Anesthesiologists score greater than 3, long-term oral corticosteroid therapy, a medical contraindication to corticosteroids, or inability to adhere to the medical follow-up.

Randomization and Masking

Eligible patients were randomized to 1 of 2 groups by the investigator the day before surgery using the secure online CleanWeb platform (Telemedicine Technologies S.A.S) with a 1:1 ratio. The experimental (corticosteroid) group received 20 mg/kg of methylprednisolone intravenously at the time of anesthesia induction and the control (placebo) group received an intravenous placebo with an identical appearance.

Both solutions were prepared by the hospital pharmacy. Randomization was based on a stratification algorithm implemented on the CleanWeb platform. Random allocation was stratified by center, the location of the cancer (upper gastrointestinal tract, biliopancreatic, small bowel, or colorectal), and the scheduled surgical approach (minimally invasive or open surgery). All members of the anesthesiology and surgical team and involved caregivers were blinded to random allocation sequences and group assignments, as were the investigator and the staff managing the patient and recording the outcomes. Blinding was maintained throughout the study.

Procedures

According to group assignment, methylprednisolone or placebo was administered at anesthesia induction. Patients with diabetes in both groups had close monitoring of their capillary glycemia during and immediately after surgery. The surgical protocol was unaffected by inclusion in the study. The usual preventive measures regarding surgical-site infections, urinary tract infections and nosocomial infections (including the antibioprophylaxis policy) were applied according to current French guidelines and were unaffected by the participation in the trial. Postoperative management adhered to each hospital's current practice.

End Points

The primary end point was the frequency of major postoperative complications occurring within 30 days after surgery. Complications were defined as major according to a Clavien-Dindo grade greater than 2 as follows: complications requiring any surgical, endoscopic, or radiological intervention or associating organ failure with intensive care readmission or death.[16]

Secondary efficacy end points included postoperative infections, intra-abdominal infections (including anastomotic fistula and intra-abdominal abscess) within 30 days after surgery according to the Centers for Disease Control and Prevention definition, wound infection before POD30, the hospital LOS after surgery, and the quality of wound healing assessed by the surgeon at POD30. In case of death, patients were considered to have been hospitalized until POD30.

Safety end points included the frequency of postoperative metabolic disorders, defined as hyperglycemia or electrolyte disorders and assessed by blood samples within the first 24 postoperative hours. Hyperglycemia was classified as mild (between 99.15 and 160.4 mg/dL; to convert glucose to millimoles per liter, multiply by 0.0555), moderate (between 160.5 and 250.5 mg/dL), severe (between 250.6 and 500.9 mg/dL), and life-threatening (>500.9 mg/dL). Adverse events, serious adverse events, and unexpected adverse events were assessed daily and recorded according to current regulations.

After routine data monitoring by a research technician, an adjudication board composed of a surgeon and an anesthesiologist, both independent of the investigators and sponsor and blinded to patient allocation, randomly reviewed 20% of records, as well as all records with incoherent data regarding the primary and secondary end points. If the adjudication committee reached the same conclusion as the investigators for all patients reviewed from a center, no further reviews were pursued in that center. In case of discrepancies, the end points were reviewed for all patients included in that center. Reviewed data included clinical data, laboratory results, medical imaging, outcomes and all other relevant data.

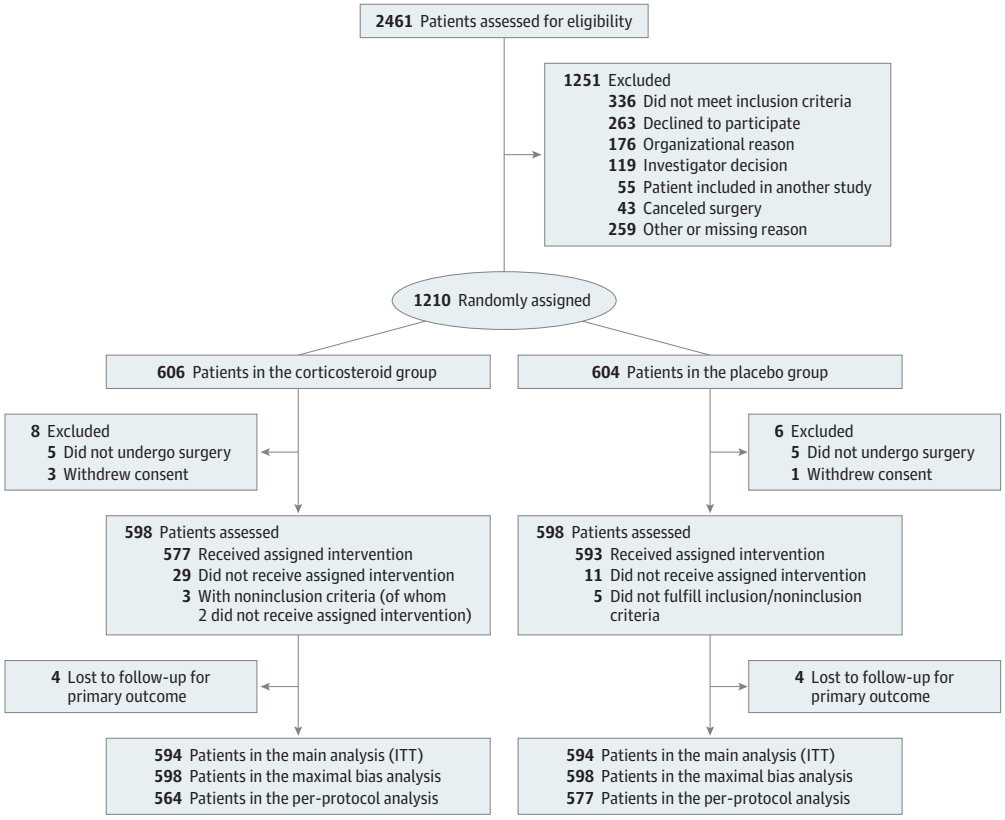
Statistical Analysis

Considering major complications after surgery as a binary outcome, we hypothesized, based on the current literature, that there would be a decrease from 26% (placebo group) to 18% (treatment group). Estimating that 5% of patients would have missing values precluding inclusion in the definitive analysis, 1200 randomized patients (600 per arm) were required to obtain 1184 analyzable patients (592 per arm), providing 90% power with a 2-sided α level of .05; 1 interim efficacy and safety analysis was planned after the inclusion of 592 patients (296 per arm), using an O'Brien-Fleming α-spending rule.[17] As criteria for early termination of the study were not met, the trial continued until the scheduled end of inclusions.

Efficacy analyses were performed according to the intention-to-treat (ITT) principle. For the main outcome, patients lost to follow-up were analyzed under the maximal bias analysis (postoperative major complications in patients receiving corticosteroids and no major complications in patients receiving placebo) and then excluded in the full analysis set. There was no influence on the results of our main analysis considering that they represented less than 1% of randomized patients. The main analysis was completed using a per-protocol analysis, excluding patients with no administered treatment or major protocol deviation. Categorical variables were expressed as numbers and percentages; continuous variables were expressed as means and SDs or medians and IQRs, as appropriate. Both categorical and continuous variables were compared in bivariate analyses with the use of corresponding tests. The proportion of patients with major postoperative complications at POD30 were compared between groups using the χ^2 test. This analysis was completed using logistic regression stratified on the center and adjusted for baseline factors (the surgery site and exposure or not to dexamethasone for the prevention of postoperative nausea and vomiting). Subgroup analyses according to surgery site and the primary cancer were performed for exploratory purposes.

Regarding secondary outcomes, the proportion of patients with postoperative infections, intra-abdominal infections, wound infections, and nosocomial infections at POD30 were compared using the χ^2 test. The LOS in days until POD30 was expressed as medians and IQRs and was compared using the Mann-Whitney *U* test. Wound healing was considered to be satisfactory if the clinical inspection revealed no disunion, hypertrophy, or keloid. The effect of a pulse dose of corticosteroids on outcomes was expressed as odds ratios (ORs) with 95% CIs for categorical variables, and as mean differences with 95% CIs for continuous variables. Regarding safety outcomes, the percentage of patients with hyperglycemia and electrolyte disorders were compared between groups with the use of the χ^2 test or the Fisher test, as appropriate. Analyses were performed with SAS software, version 9.4 (SAS Institute Inc). The significance level was set at .05 for all analyses.

Figure. Flowchart of the Benefit of a Flash Dose of Corticosteroids in Digestive Surgical Oncology: a Randomized, Double-Blind, Placebo-Controlled Trial (CORTIFRENCH)



ITT indicates intention to treat.

Results

Between July 1, 2019, and December 31, 2023, a total of 2461 patients were referred for major digestive surgery. Among these, we enrolled 1228 patients from 23 French hospitals. Overall, 1210 patients (mean [SD] age, 65.9 [11.3] years; 448 female [37%]; 762 male [63%]) were randomized (606 in the corticosteroid group and 604 in the placebo group), of whom 10 did not have surgery and 9 withdrew consent and were excluded. Forty-seven patients had major deviations to protocol and were excluded from the per-protocol analysis. Eight patients were lost to follow-up at hospital discharge between 6 and 18 days after surgery, without any severe complication at hospital discharge, and were equally distributed between both arms. Among the 1196 remaining patients, 1188 were included in the ITT analysis (594 patients in each group). The flowchart of the study is presented in the **Figure**. The characteristics of the included patients and their surgery are presented in **Table 1**. Overall, the characteristics were well balanced between groups at baseline.

Regarding the primary outcome, the proportion of patients presenting major postoperative complications did not significantly differ between the 2 arms as follows: 139 of 594 patients (23%) receiving methylprednisolone vs 119 of 594 patients (20%) receiving placebo (crude OR, 1.22; 95% CI, 0.92-1.61; $P = .16$) in the ITT analysis, as well as in the maximal bias analysis (143 of 598 patients [24%] vs 119 of 598 patients [20%], respectively; OR, 1.26; 95% CI, 0.96-1.66; $P = .09$). Logistic regression stratified on the center and adjusted for surgery site and exposure to dexamethasone for postoperative nausea and vomiting prevention yielded similar results (adjusted OR, 1.20; 95% CI, 0.91-1.60; $P = .20$). A subgroup analysis according to the primary cancer type and surgery location (upper gastrointestinal, colorectal, or biliopancreatic) found no differences in the primary outcomes (**Table 2**).

The results of the per-protocol analysis including 1141 patients were consistent as follows: major complications occurred in 250 of 1141 patients (22%) overall (134 of 564 [24%] in the corticosteroid arm vs 116 of 577 [20%] in the placebo arm; $P = .14$). Seventy-nine patients underwent reoperation in the 30 days after surgery in the corticosteroid group (13%) vs 67 (11%) in the placebo group ($P = .29$). Fifteen patients died in the 30 days after surgery in the corticosteroid group (2.4%) vs 8 (1.4%) in the placebo group ($P = .14$).

Regarding the other outcomes of the 594 patients in each study arm, there was no significant difference in the rate of postoperative infections (182 [31%] vs 177 [30%]; OR, 1.04; 95% CI, 0.81-1.33; $P = .75$), intra-abdominal infections (142 [24%] vs 126 [21%]; OR, 1.17; 95% CI, 0.89-1.53; $P = .27$), wound

Table 1. Baseline Characteristics of Patients in Both Groups[a]

Characteristic	Patients, No. (%)	
	Corticosteroid (n = 594)	Placebo (n = 594)
Age, y		
Mean (SD)	66 (12)	66 (11)
Range	21-94	19-94
Sex		
Female	229 (39)	211 (36)
Male	365 (61)	383 (64)
ASA score		
1	57 (10)	48 (8)
2	312 (53)	319 (54)
3	225 (38)	227 (38)
Smoking		
No	514 (87)	501 (84)
Yes	80 (13)	93 (16)
Previous thromboembolic disease	59 (10)	71 (12)
Previous coronary disease or stroke	77 (13)	78 (13)
Previous chronic pulmonary disease	32 (5)	40 (7)
Diabetes	127 (21)	111 (19)
Chronic liver disease (cirrhosis)	11 (2)	9 (2)
Previous history of cancer (extra-digestive)	20 (3)	27 (5)
Preoperative immunonutrition	389 (65)	383 (64)
Preoperative radiotherapy (within 2 mo)	23 (4)	24 (4)
Preoperative chemotherapy (within 2 mo)	91 (15)	104 (18)
Preoperative PCT, mean (SD), ng/mL	0.14 (0.37)	0.21 (1.34)
Preoperative CRP mean (SD), mg/dL	0.91 (1.56)	1.03 (1.92)
Preoperative albuminemia mean (SD), g/dL	3.89 (0.46)	3.93 (0.49)
Primary digestive cancer		
Esophagus	34 (6)	38 (6)
Stomach	53 (9)	48 (8)
Duodenum	10 (2)	18 (3)
Biliopancreatic	204 (34)	196 (33)
Small bowel	17 (3)	18 (3)
Colorectal	281 (47)	280 (47)
Concomitant liver metastases treated	26 (4)	28 (5)
Surgical approach		
Open surgery	336 (56)	324 (55)
Minimally invasive	258 (43)	269 (45)
Duration of surgery, mean (SD), h	4.7 (2.2)	4.6 (2.2)
Dose of dexamethasone for PONV prevention, mean (SD)	7.81 (0.85)	7.84 (0.95)
Blood loss >500 mL	102 (17)	104 (17)
Intraoperative transfusion	32 (5)	32 (5)
Insulin requirement during surgery	48 (8)	40 (7)

Abbreviations: ASA, American Society of Anesthesiologists; CRP, C-reactive protein; PCT, procalcitonine; PONV, postoperative nausea and vomiting.

SI conversion factor: To convert CRP to milligrams per liter, multiply by 10; albumin to grams per liter, multiply by 10.

[a] Benefit of a Flash Dose of Corticosteroids in Digestive Surgical Oncology: a Randomized, Double-Blind, Placebo-Controlled Trial (CORTIFRENCH) trial full analysis set (intention to treat).

infections (34 [6%] vs 28 [5%]; OR, 1.23; 95% CI, 0.73-2.05; P = .43), nosocomial infections (68 [11%] vs 62 [10%]; OR, 1.11; 95% CI, 0.77-1.6; P = .58), LOS (mean [SD], 13.21 [8.59] days vs 12.97 [8.1] days, P = .93), the need for reoperation (79 [13%] vs 67 [11%]; OR, 1.21; 95% CI, 0.85-1.71; P = .29), or wound healing (87 [15%] vs 69 [12%]; OR, 1.31; 95% CI, 0.93-1.83; P = .13) in the 30 days after the operation. Postoperative C-reactive protein levels were significantly lower in the corticosteroid group on POD 1 (mean [SD], 5.81 [3.43] mg/dL vs 6.76 [3.82] mg/dL; OR, 0.95; 95% CI, 0.44-1.47; P <.001; to convert C-reactive protein to milligrams per liter, multiply by 10) and POD 3 (mean [SD], 8.85 [7.80] mg/dL vs 14.89 [8.47] mg/dL; OR, 6.05; 95% CI, 4.81-7.29; P <.001) (**Table 3**). The subgroup analysis according to the primary cancer type and surgery location (upper gastrointestinal, colorectal, or biliopancreatic) did not find any significant difference in these secondary outcomes.

In terms of safety, patients in the corticosteroid group experienced more episodes of moderate hyperglycemia (160.4-250.5 mg/dL) in the 48 hours after surgery: 137 patients (23%) vs 108 patients (18%; P = .03). There was no difference in the onset of mild, severe, or life-threatening hyperglycemia. Similar results were observed for hyperglycemia between POD1 and POD10. The rate of clinically significant electrolytic disorders was similar in the 2 groups. Adverse events according to organ classes and severity are detailed in the eTable in Supplement 2.

Discussion

In our study, the administration of a single pulse dose of methylprednisolone (20 mg per kilogram) during anesthesia induction before digestive cancer surgery was not beneficial in terms of morbidity or patient recovery. It had no impact on specific surgical outcomes, such as major complications, anastomotic leakage, intra-abdominal infection, overall postoperative infection, wound infection, wound healing, or LOS.

It is well established that a preoperative pulse dose of corticosteroids can attenuate the postoperative inflammatory response, both in elective and emergency surgery.[12,18-21] Although this effect is confirmed by our results, the clinical benefit is not clearly established.

In cardiac surgery, a randomized clinical trial[22] including 1263 infants did not find improved outcomes after a pulse dose of 30 mg/kg of methylprednisolone. Similar results were obtained in a randomized clinical trial[23] including more than 7500 adults undergoing cardiopulmonary bypass and comparing methylprednisolone (250 mg at anesthetic induction and 250 mg at initiation of cardiopulmonary bypass) with placebo.

In major noncardiac surgery, a double-blind placebo-controlled randomized clinical trial[24] including 1222 patients found no benefit after the administration of 0.2 mg/kg of dexamethasone immediately after the surgical procedure and on day 1. This trial included different types of surgery as follows: 65% of patients were operated on for cancer and 63% underwent abdominal operations. The primary end point, a composite of severe morbidity and mortality, was not significantly affected. The fact that these large, placebo-controlled,

Table 2. Primary Outcome in the Main Analysis (ITT Principle, Full Analysis Set) on All Patients and According to the Intervention Level

Outcome	No./total No. (%)		Unadjusted OR (95% CI)	*P* value
	Methylprednisolone	Placebo		
Major postoperative complication within 30 d after surgery				
All patients	139/594 (23)	119/594 (20)	1.22 (0.92-1.61)	.16
Type of surgery				
Upper GI	31/95 (33)	28/99 (30)	1.23 (0.67-2.27)	.51
Colorectal	49/298 (16)	49/300 (16)	1.01 (0.65-1.55)	.97
Biliopancreatic	59/201 (29)	42/195 (22)	1.51 (0.96-2.39)	.07

Abbreviations: GI, gastrointestinal; ITT, intention to treat; OR, odds ratio.

Table 3. Secondary and Other Efficacy Outcomes Within 30 Days After Surgery in the Main Analysis (ITT Principle, Full Analysis Set)

Outcome	No./total No. (%)		Unadjusted OR (95% CI)	*P* value
	Methylprednisolone	Placebo		
Postoperative infections[a]	182/594 (31)	177/594 (30)	1.04 (0.81 to 1.33)	.75
Intra-abdominal infections[a]	142/594 (24)	126/594 (21)	1.17 (0.89 to 1.53)	.27
Anastomotic leakage[a]	129/594 (22)	110/594 (19)	1.22 (0.92 to 1.62)	.17
Wound infection	34/594 (6)	28/594 (5)	1.23 (0.73 to 2.05)	.43
Unsatisfactory wound healing	87/594 (15)	69/594 (12)	1.31 (0.93 to 1.83)	.13
Nosocomial infections (urinary, pulmonary or catheter related)[a]	68/594 (11)	62/594 (10)	1.11 (0.77 to 1.6)	.58
Length of stay after surgery, mean (SD), d[b]	13.21 (8.59)	12.97 (8.1)	0.24 (−22.9 to 23.38)[c]	.93
			Unadjusted mean difference (95% CI)	
CRP, mean (SD), mg/dL				
Baseline	0.91 (1.56)	1.03 (1.92)	0.12 (0.13-0.36)	.34
Day1	5.81 (3.43)	6.76 (3.82)	0.95 (0.44-1.47)	<.001
Day3	8.85 (7.80)	14.89 (8.47)	6.05 (4.81-7.29)	<.001

Abbreviations: CRP, C-reactive protein; ITT, intention to treat; OR, odds ratio.

SI conversion factor: To convert CRP to milligrams per liter, multiply by 10.

[a] Anastomotic leakages are all included in intra-abdominal infections. Intra-abdominal infections are included in postoperative infections. Nosocomial infections and wound infections are both included within postoperative infections.

[b] Patients who died within 30 days were considered to have been hospitalized until postoperative day 30.

[c] Nonadjusted mean difference (95% CI).

randomized clinical trials obtained results consistent with our study, also involving a high dose of corticosteroids, suggests that preoperative corticosteroids provide no benefit in terms of morbidity.

On the contrary, in a study[20] focusing on total hip arthroplasty, the decrease in the inflammatory markers obtained with perioperative corticosteroids reduced the LOS, pain, and opioid consumption, although it did not improve postoperative complications. In patients undergoing major hepatic surgery, there appears to be an established benefit after a preoperative pulse dose of corticosteroids, including improved tolerance to vascular clamping and fewer surgical infections and postoperative complications, thus reducing LOS.[12,25-27] In some trials involving other types of digestive surgery, a preoperative pulse dose of corticosteroids reduced postoperative morbidity (surgical infections, postoperative pain, cognitive impairment), improved recovery, and shortened LOS. After pancreatoduodenectomy, postoperative morbidity was decreased when patients received 100 mg of hydrocortisone, whereas no benefit was found in patients receiving 0.2 mg/kg of dexamethasone.[28,29] In patients who received 125 mg of methylprednisolone for abdominal wall reconstruction, Jensen et al[30] found a decrease in postoperative pain during activity and coughing but no benefit for pain at rest. Despite the lack of scientific evidence regarding clinical benefit, a decrease in postoperative morbidity has been suggested in patients undergoing colorectal surgery receiving perioperative steroids, resulting in the increasing use of this treatment in some countries.[31] In the context of emergency laparotomy, a single study[18] reported that survival was improved (23% vs 7%, 90-day mortality rate) with a single preoperative dose of dexamethasone (1 mg/kg). A recent meta-analysis[32] of perioperative corticosteroids in esophagectomy suggested a decrease in some end points (cardiovascular events, general complications, and length of intensive care unit stay) but no impact on major outcomes (leakage, mortality, or LOS). Several other trials[33,34] reported no significant benefit after gastrectomy or appendectomy despite using equivalent doses of corticosteroids. In the current CORTIFRENCH trial, the number of patients included for each digestive surgery type (upper gastrointestinal, colorectal, and biliopancreatic) exceeded the number of patients included in any of the previous trials. The dose of methylprednisolone used was also higher.

The CORTIFRENCH trial focused on digestive cancer surgery, excluding patients undergoing hepatic resection alone. This exclusion was based on the specific benefit related to vascular clamping tolerance, which may have introduced a bias in the results. Moreover, hepatectomy

complications are less frequently infectious than in digestive tract surgery.

The CORTIFRENCH trial was a pragmatic trial that did not modify the usual perioperative care in each participating center. Stratification by center was performed to prevent bias in terms of postoperative outcomes due to differences in perioperative management. Each type of digestive surgery is associated with specific complications (more frequent respiratory complications in esophageal surgery, a higher rate of anastomotic leaks in pancreatic surgery, and more frequent surgical-site infections in colorectal surgery). A stratification by type of surgery aimed to minimize the risk that any single type (particularly colorectal cancer surgery, which was the most frequent) could bias the overall results. However, the subgroup analysis did not reveal any differences depending on the type of surgery (upper gastrointestinal, colorectal, or biliopancreatic).

Although some small trials focusing on inflammatory markers and a variety of clinical end points have suggested a benefit for preoperative corticosteroids, our results are consistent with those of previous large randomized trials in various fields of surgery.[22-24] Corticosteroids do decrease perioperative inflammation after digestive cancer surgery, as evidenced here by the lower postoperative CRP levels in the group receiving corticosteroids, but this did not lead to a clinical benefit. As postoperative pain was not evaluated in the trial, we cannot conclude on an eventual benefit on this point. In our view, this trial provides strong evidence against the hope that corticosteroids can reduce severe postoperative morbidity or improve postoperative recovery.

Regarding oncologic implications, we have no data on 3-year survival yet. A recent trial[34] evaluating 5 mg/kg of methylprednisolone at the beginning of gastrectomy for cancer did not find a benefit in recurrence-free survival at 3 years (primary end point), but the subgroup analysis suggested a potential benefit in some histological types or stages.

Future advances will likely come from multimodal approach to prehabilitation associating pharmacological, nutritional, and psychological approaches as well as adapted physical activity.[35]

Limitations

One limit of our study was the possibility of unblinding due to steroid effects (hyperglycemia, namely in patients without diabetes, or hypokalemia). Although this was a real possibility for the staff treating the patient, the risk of its influence in the record of robust end points such as severe morbidity, postoperative infections, or the LOS is very low. Unblinding could have influenced the perception of the quality of wound healing at POD30, but the surgeon who evaluated this end point was unlikely to have managed the postoperative metabolic disorders of the patient due to the organization of perioperative care in France (metabolic disorders are mainly managed by anesthesiologists, especially before POD2).

Conclusions

In conclusion, results of the CORTIFRENCH randomized clinical trial provided strong evidence against the systematic use of a single pulse dose of perioperative steroids in elective digestive cancer surgery. The long-sought pharmacological holy grail for the prevention of postoperative complications—if it exists at all—remains to be discovered.

ARTICLE INFORMATION

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