Surgery 167 (2020) 757–764

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Preoperative, single, high-dose glucocorticoid administration in abdominal wall reconstruction: A randomized, double-blinded clinical trial

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ARTICLE INFO

Article history:
Accepted 6 December 2019
Available online 13 February 2020

ABSTRACT

Background: Although preoperative administration of high-dose glucocorticoid may lead to improved recovery after operative procedures, this regimen has not been examined in patients undergoing abdominal wall reconstruction for repair of large ventral hernias. The aim of the current trial was to examine the effects of preoperative, single high-dose glucocorticoid on recovery after abdominal wall reconstruction.

Method: Forty patients undergoing abdominal wall reconstruction for repair of ventral incisional hernias with a horizontal fascial defect >10 cm were randomized to intravenous administration of either 125 mg methylprednisolone or placebo at the induction of anesthesia. The primary endpoint was pain in the supine position as assessed by a numeric rating scale of 0 to 10 at rest at 8 am on the first postoperative day. Secondary outcomes included postoperative pain during activity, nausea, fatigue, inflammatory response (measured by plasma levels of C-reactive protein), duration of stay, and 30-day complications or readmissions.

Results: There was no difference in pain at rest on the first postoperative day (methylprednisolone mean 1.7 vs placebo 2.2, $P > .95$), whereas patients in the methylprednisolone group reported less pain during activity (mean 3.0 vs 5.0; $P = .011$) and during coughing (3.4 vs 5.9; $P = .010$). There were no differences between the 2 groups regarding postoperative fatigue or nausea. Postoperative levels of C-reactive protein were less in the methylprednisolone group ($P = .039$).

Conclusion: A single-shot, high-dose methylprednisolone before abdominal wall reconstruction for a large incisional hernia decreased early postoperative pain and attenuated the inflammatory response.

Introduction

Abdominal wall reconstruction (AWR) for large ventral incisional hernias is associated with high rates of postoperative complications and prolonged durations of stay.[1,2] Patients undergoing AWR are often subjected to a full laparotomy, complete adhesiolysis, and component separation with wide dissection of the abdominal wall making the analgesic treatment of this patient group a challenge. Consequently, the need remains for optimization of postoperative recovery.[3]

Preoperative, single-shot, systemic administration of glucocorticoids has been shown advantageous across different surgical disciplines. Besides attenuating the systemic inflammatory response, such therapy decreases postoperative pain, nausea, and vomiting without noticeable negative side effects.[4–9] Thus, administration of glucocorticoids may prove valuable for optimization of recovery after AWR. Because systemic administration of perioperative glucocorticoid has not been tested specifically in this setting,[10] the current study aimed at examining the effect of preoperative administration of glucocorticoid versus placebo on the recovery after AWR.

Presented at the Danish Hernia Database yearly meeting, Copenhagen, Denmark, May 13, 2018.

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https://doi.org/10.1016/j.surg.2019.12.007
0039-6060/

Table I
In- and exclusion criteria

Inclusion criteria
Age ≥18 y
Ventral incisional hernia with a horizontal fascial defect ≥10 cm described at either clinical examination or computed tomography
Planned elective open hernia repair
Ability to speak and understand Danish
Ability to give written and oral informed consent
Exclusion criteria
Daily use of systemic glucocorticoid medication*
Body mass index ≥35 kg/m^2
Tobacco smoking within 6 weeks before surgery
Heart disease (New York Heart Association class 3–4)*
Chronic renal failure (glomerular filtration rate <60 mL/min per 1.73 m^2)*
Insulin dependent diabetes*
Excessive use of alcohol*
Known allergy to MP*
Planned pregnancy within 3 months postoperatively*
Positive pregnancy test†
Actively treated peptic ulcer disease within one month preoperatively†

* Evaluated at scheduling of surgery.
† Evaluated within 1 week preoperatively.

Methods

Trial design and participants

This single-center, double-blinded, placebo controlled randomized trial with a 1 to 1 allocation ratio examined the effects of preoperatively administered methylprednisolone (MP) in patients undergoing AWR. The study protocol for this trial has been published previously.[11]

Patients eligible for the current study were those undergoing elective AWR for a ventral incisional hernia with a horizontal fascial defect ≥10 cm described at either clinical examination or preoperative computed tomography. Inclusion and exclusion criteria are shown in Table I. Patients were screened for inclusion in the outpatient clinic of the university hospital where the study was undertaken from March 2016 to May 2018.

Randomization, intervention, and blinding

An independent physician performed the randomization using a computer-generated sequence with varying block sizes, involving preparing sealed envelopes. Based on randomization, another physician not otherwise involved in the study prepared either the study medication or the placebo and administered it to the patient during induction of anesthesia. Patients, data collectors, and medical staff involved in the treatment of patients were blinded to the study allocation. Every dropout who did not contribute to the study with the primary outcome were replaced with a patient using the same allocation and blinding. The study intervention consisted of intravenous administration of 125 mg MP (Solu-medrol; Pfizer, Ballerup, Denmark) compared with placebo (154 mM NaCl).

Standard perioperative treatment

The day of operation was defined as day 0. All patients were evaluated at a preoperative, multidisciplinary, hernia conference. Preoperative optimization consisted of complete smoking cessation for at least 6 weeks and weight loss until body mass index was below 35 kg/m^2. One hour preoperatively (day 0), acetaminophen 1 g, ibuprofen 600 mg, and gabapentin 600 mg were administered orally. For thromboprophylaxis, Thrombo-Embolus Deterrent stockings were applied before the operation, and the first dose of once daily, subcutaneous low-molecular weight heparin (tinzaparin 3,500 to 4,500 IU) was administered immediately after placement of the epidural catheter. Preoperative antibiotics consisted of cefuroxime 1.5 to 2.25 g intravenously (repeated intraoperatively every 3 hours) and gentamicin 5 mg/kg intravenously (single shot).

An epidural catheter was placed preoperatively in the relevant vertebral interspace according to the hernia location, most often Th 7 or 8. Intraoperative epidural infusion consisted of 4 to 6 mL/h of a solution of bupivacaine 0.25% and morphine 0.2 mg/mL. Anesthesia was induced with propofol and remifentanil and maintained with propofol or sevoflurane. Muscle relaxation was achieved by rocuronium.

Operative technique

All patients underwent open surgery including laparotomy, lysis of adhesions to the anterior abdominal wall, and retromuscular dissection consistent with the Rives-Stoppa approach. Endoscopic, anterior component separation or open transversus abdominis release was performed if indicated.[12] Reconstruction of the posterior rectus sheath was performed using a continuous, slowly resorbable suture (Monomax 2–0; B Braun, Melsungen, Germany) monofilament suture with placement of a self-gripping mesh (Parietex ProGrip; Sofradim Production, Trevoux, France) in the retromuscular space. This mesh is a large-pore, moderate-weight, polyester mesh with resorbable polylactic acid grips on 1 side for fixation. After retro-rectus mesh placement, the linea alba was reconstructed with a 2-0 continuous monofilament suture followed by subcutaneous placement of 1 or 2 14F drains and skin closure. An abdominal binder was applied immediately after skin closure.

Postoperative care

Postoperative analgesia was achieved with orally administered acetaminophen 1 g every 6 hours and ibuprofen 400 mg every 8 hours, as well as epidural infusion of 4 to 6 mL/h containing bupivacaine 0.25% and morphine 0.2 mg/mL. Epidural analgesia was discontinued on postoperative day 2 at 9 pm, and the epidural catheter was removed on the morning of postoperative day 3. One hour before the cessation of epidural analgesia, morphine 10 mg was administered orally as analgesic bridging. Rescue analgesics consisted of either orally or intravenously administered morphine or oxycodone.

Early oral feeding was begun as tolerated immediately postoperatively. Patients were mobilized from the bed postoperatively as soon as possible, preferably on returning from the recovery ward. Pulmonary physiotherapy was initiated within 24 hours postoperatively. Drains were removed when the daily output was <60 mL per drain.

Outcomes

The study outcomes were divided into subjective and objective outcomes. The patients registered all subjective outcomes on postoperative days 0 to 5, starting at 8 pm (±1 hour) on the day of operation, at 8 am (±1 hour) and 8 pm (±1 hour) on the next 5 days, as well as at the 30-day follow-up. All subjective outcomes were registered on a from 0 (no symptoms) to 10 (worst symptoms) scale. The numeric rating scale is a valid tool for the assessment of pain, shown to be more sensitive compared with visual analog scales and verbal rating scales.[13] The subjective outcomes were reported in figures depicting the mean (standard error) on postoperative mornings and evenings.

The primary outcome of the study was self-reported pain at rest in the supine position at 8 am (± 1 hour) on the first postoperative day. Secondary outcomes were pain immediately after moving

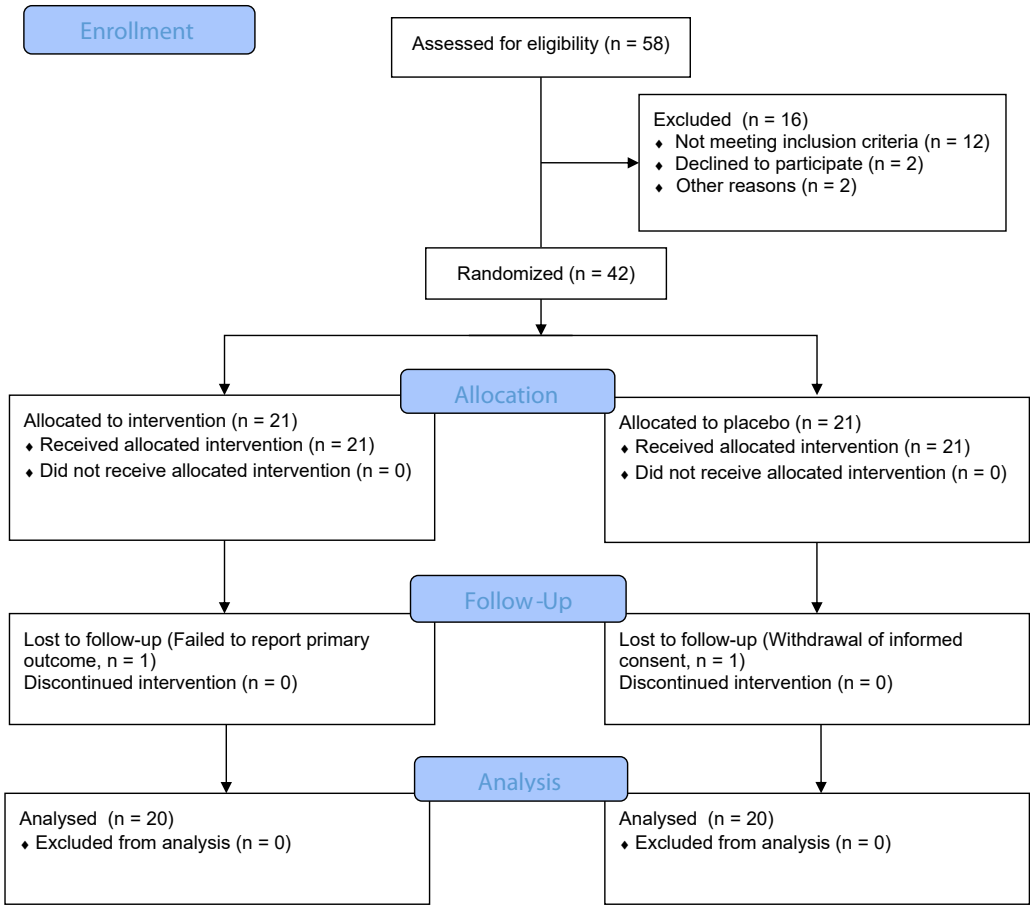

Fig 1. Consort flow diagram.

from supine to sitting position and pain when coughing, while nausea and fatigue as well as the presence or absence of vomiting were evaluated each day. Objective outcomes were registered by a study nurse and included wound drain output on postoperative day 1, the need for rescue analgesics and anti-emetics during the first 3 postoperative days, the rate of wound complications (surgical site infection, skin necrosis, skin dehiscence, hematoma, and seroma), the time from end of operation to discharge, readmissions, and surgical re-interventions.

Serum levels of C-reactive protein (CRP) were measured preoperatively and on postoperative days 1 to 3 at 8 am (±1 hour).

Statistics and sample size calculation

The sample size calculation for the current study was based on a pilot study including 10 patients undergoing AWR after a similar indication and treatment algorithm. The mean self-reported pain on the numeric rating scale on the first postoperative day was 3.6 (standard deviation [SD] 1.3). Considering a 25% decrease in pain as clinically relevant, a total of 36 patients (18 in each group) were required to obtain 80% power at a significance level of 5%.

Continuous measures were reported as medians (interquartile range [IQR]) or mean (SD) and compared across treatment groups with Wilcoxon's signed-rank test or Student's *t*-test, according to the distribution of data. Categorical parameters were compared across groups by Fisher exact test. *P* values <.05 were considered statistically significant. Pain, fatigue, and nausea scores as well as postoperative CRP levels were analyzed using repeated measurement, mixed effect regression, and presented as a Wald χ^2 test for overall differences between the 2 groups. All statistical analyses were undertaken using R 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

This study was conducted in accordance with the principles of Good Clinical Practice and monitored by the Good Clinical Practice authority of the Copenhagen University Hospital. Approval was obtained by the Danish Data Protection Agency (ref. BFH-2015-076), the Research Ethics Committee of Copenhagen (Protocol

Table II
Demographics of patients available for analysis of efficacy

Variable	MP group ($n = 20$)	Placebo group ($n = 20$)	*P*
Age, y	64.3 [10.6]	60.9 [14.6]	.386
Female	9 (45.0)	9 (45.0)	1.00
Body mass index, kg/m^2	28.7 [4.5]	27.0 [4.2]	.203
ASA score			.409
1	5 (25.0)	3 (15.0)	
2	14 (70.0)	17 (85.0)	
3	1 (5.0)	0 (0.0)	
Hypertension	10 (50.0)	7 (35.0)	.522
Heart disease	1 (5.0)	2 (10.0)	1.00
Pulmonary disease	3 (15.0)	3 (15.0)	1.00
Diabetes	1 (5.0)	0 (0.0)	1.00
Former tobacco smoker	11 (55.0)	15 (75.0)	.320
Number of previous hernia repairs			.171
0	12 (60.0)	17 (85.0)	
1	4 (20.0)	3 (15.0)	
2	2 (10.0)	0 (0.0)	
3	2 (10.0)	0 (0.0)	

Data are given as *n* (per cent) and mean [standard deviation].
ASA, American Society of Anesthesiologists.

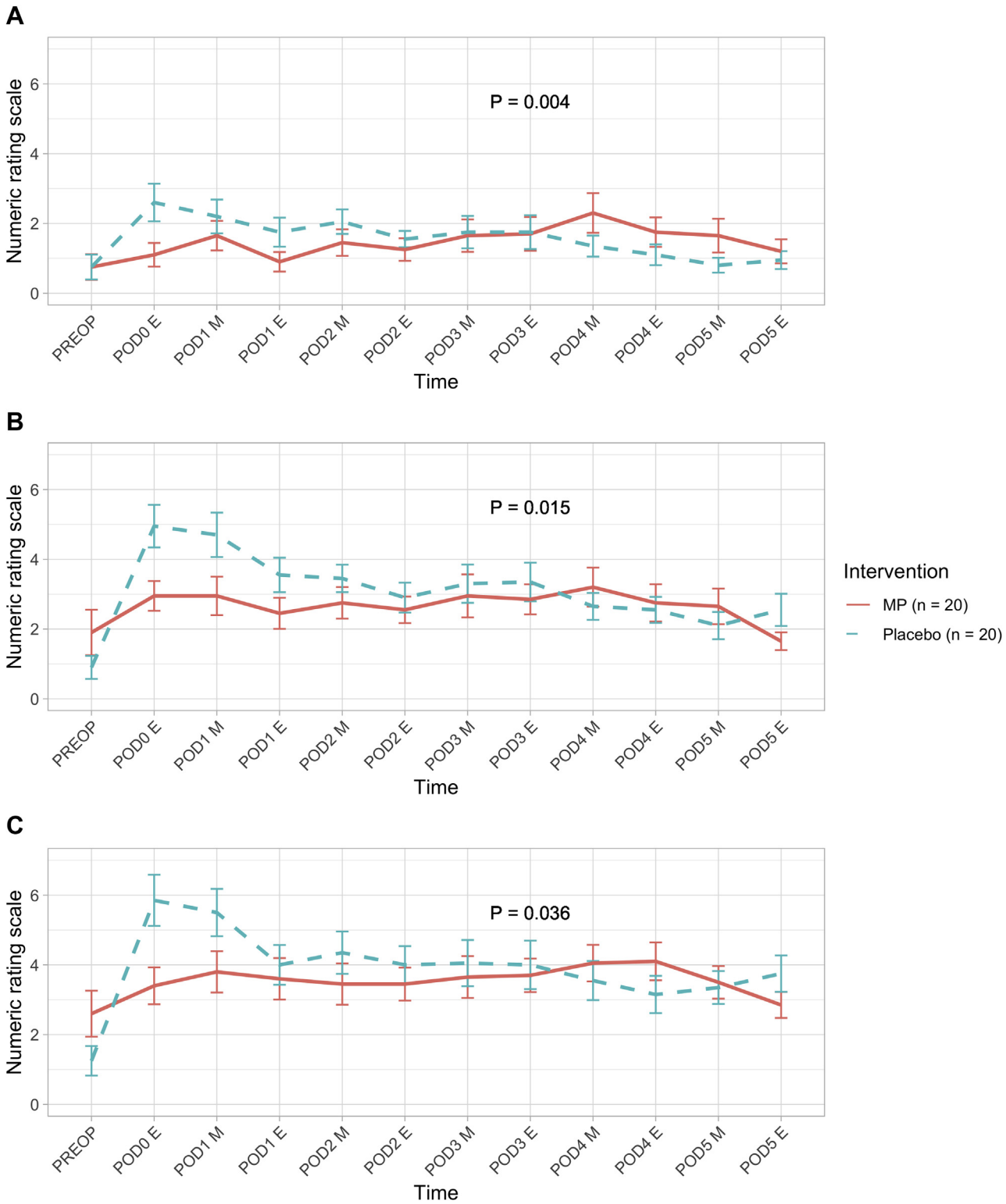

Fig 2. Mean pain on a numeric rating scale ranging from 0 (none) to 10 (worst imaginable) after abdominal wall reconstruction in patients preoperatively treated with either 125 mg MP or placebo. At rest in supine position (*A*), when moving from supine to sitting position (*B*), and when coughing (*C*). Bars indicate standard error of the means. *E*, evening 7–9 PM; *M*, morning 7–9 AM; *POD*, postoperative day; *PREOP*, preoperative.

No. H-2015-15017445), and the Danish Health and Medicines Authority (2015-004916-39). The study was registered at Clinicaltrials.gov (NCT no 02594241) and EudraCT (2015-004916-39). The manuscript was written in accordance with the CONSORT statement.[14]

Results

A total of 42 patients were randomized, including 2 who subsequently dropped out of the study owing to postoperative cardiac arrest requiring postoperative intensive care therapy (unable to

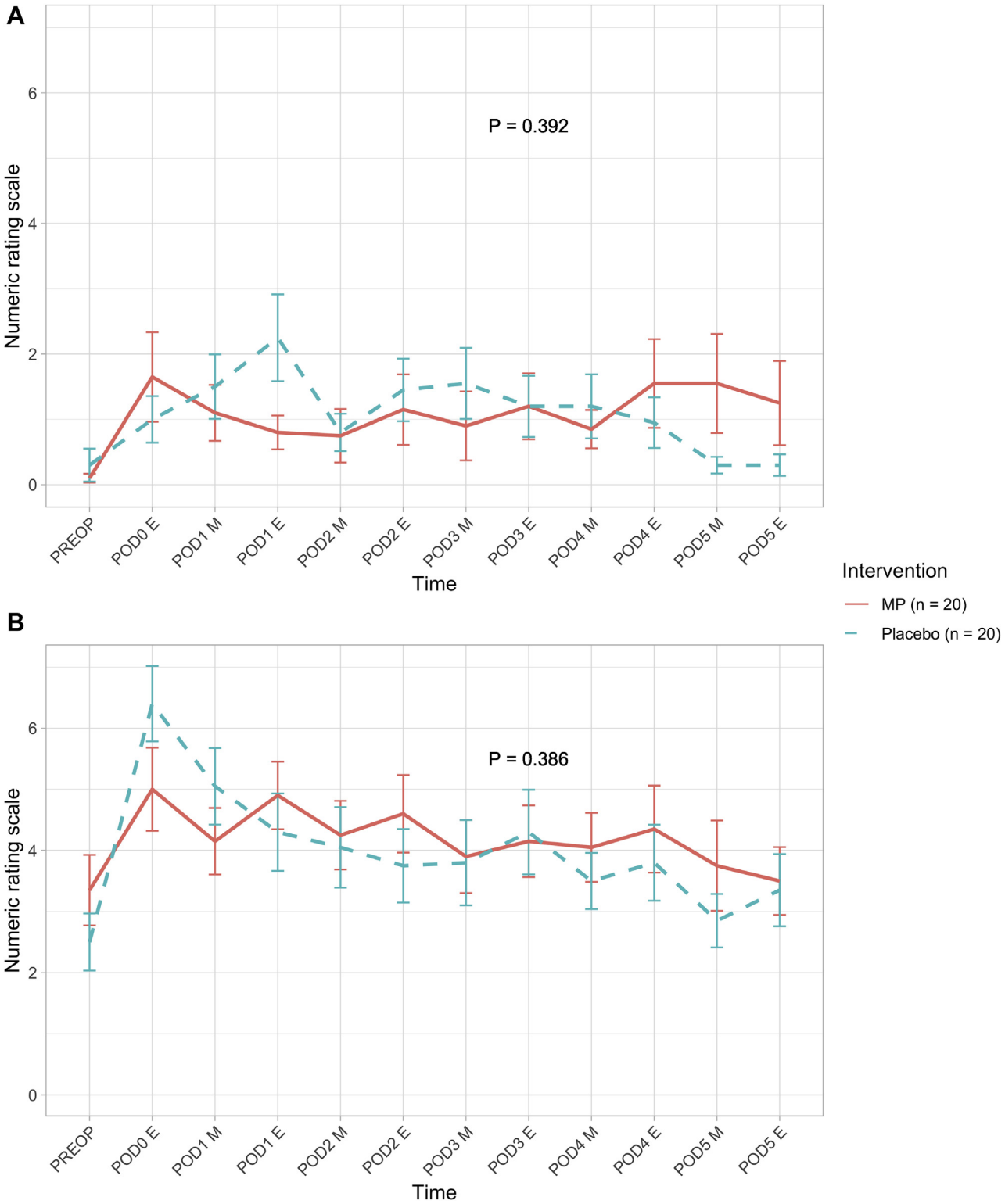

Fig 3. Mean nausea (*A*) and fatigue (*B*) on a numeric rating scale ranging from 0 (none) to 10 (worst imaginable) after abdominal wall reconstruction in patients preoperatively treated with either 125 mg MP or placebo. Bars indicate standard error of the means. *E*, evening 7–9 PM; *M*, morning 7–9 AM; *POD*, postoperative day; *PREOP*, preoperative.

assess primary outcome, recovered fully) and withdrawal of informed consent, respectively (Fig 1). Thus, 40 patients were available for analysis of efficacy. For analysis of safety, 41 patients were included.

Patient demographics and operative characteristics are presented in Table II. There were no differences between the 2 allocation arms. The groups were also well-balanced considering preoperative pain, nausea, and fatigue, and none of the patients used opioids preoperatively on a daily basis (Figs 2 and 3). One patient in each group did not receive an epidural catheter owing to difficulties placing the epidural ($n = 1$) and recent use of anticoagulative therapy ($n = 1$). Intraoperative

Table III
Peri and postoperative outcomes of patients undergoing abdominal wall reconstruction for large ventral incisional hernia

Variable	MP group ($n = 20$)	Placebo group ($n = 20$)	P
Duration of surgery, min	244 (62)	229 (56)	.421
Components separation			.773
None	3 (15.0)	3 (15.0)	
ECS	8 (40.0)	11 (55.0)	
ECS/TAR	5 (25.0)	3 (15.0)	
TAR	4 (20.0)	3 (15.0)	
Horizontal fascial defect, cm	12.0 (2.0)	12.6 (2.1)	.394
Vertical fascial defect, cm	13.6 (4.7)	14.6 (3.8)	.445
Intraoperative complications			.230
Enterotomy	3 (15.0)	0 (0.0)	
Drain output POD 1, mL	72.5 [14.2–106.2]	30.0 [15.2–92.5]	.423
No. of patients requiring rescue analgesics			
POD 1	8 (40.0)	9 (45.0)	1.00
POD 2	2 (10.0)	7 (35.0)	.130
POD 3	11 (55.0)	9 (45.0)	.752
No. of patients requiring antiemetics			
POD 1	10 (50.0)	12 (60.0)	.751
POD 2	3 (15.0)	5 (25.0)	.693
POD 3	3 (15.0)	4 (20.0)	1.00
30-d wound complications	6 (30.0)	4 (20.0)	.716
Seroma	3	1	
Skin dehiscence	2	0	
Wound infection	1	3	
30-d readmission	4 (20.0)	1 (5.0)	.339
Wound-related	2	1	
Vomiting	1	0	
Gastroenteritis	1	0	
30-d surgical reintervention	2 (10.0)	0 (0.0)	.468
Superficial wound exploration	1		
Laparotomy owing to small bowel perforation	1		
Length of stay, d	4 [3–4]	4 [3–6]	.865
Time after surgery to meet discharge criteria			.320
48 h (POD 2–8 pm)	14 (70)	9 (45)	
60 h (POD 3–8 am)	1 (5)	6 (30)	
72 h (POD 3–8 pm)	3 (15)	2 (10)	
84 h (POD 4–8 am)	1 (5)	1 (5)	
96 h (POD 4–8 pm)	1 (5)	1 (5)	
108 h (POD 5–8 am)	0 (0)	1 (5)	

Data are given as *n* (per cent), mean (standard deviation) or median [interquartile range].
ECS, endoscopic components separation; *POD*, postoperative d; *TAR*, transversus abdominis release.

complications occurred in 3 patients, all of whom were in the MP group and consisted of inadvertent enterotomies in the small ($n = 2$) and large bowel ($n = 1$). These patients were treated immediately with suture of the defect without spillage of bowel contents.

There was no difference when comparing the MP and Placebo groups in mean pain level at rest in the supine position on the first postoperative day (1.7 vs 2.2; $P > .95$), whereas the MP group reported less pain during activity (3.0 vs 5.0; $P = .011$) and coughing (3.4 vs 5.9; $P = .010$). Patients in the MP group reported less pain during the first 5 postoperative days at rest in the supine position ($P = .004$), when moving from the supine to the sitting position ($P = .015$), and when coughing ($P = .036$) (Fig 2). There were no differences between the 2 groups in regard to postoperative nausea ($P = .392$), fatigue ($P = .386$), and administration of rescue analgesics or anti-emetics (Table III, Fig 3). The levels of postoperative CRP were not independently less in the MP compared with the placebo group (POD1 87 ± 44 vs 107 ± 33L $P = .099$, POD2 128 ± 64 vs 161 ± 51; $P = .068$, or POD3 105 ± 63 vs 118 ± 66; $P = .521$). Overall, the CRP was less in the MP group as compared with the control group ($P = .039$, Fig 4).

The median time to fulfillment of discharge criteria of the MP and Placebo groups (2 days [IQR: 2–3] vs 3 days [IQR: 2–3], $P = .134$) and the median duration of stay (4 days [IQR: 3–4] versus 4 days [3–6]; $P = .865$) did not differ. In addition, there was no difference in the incidences of 30-day wound complications (6 of 20 vs 4 of 20, $P = .716$), operative re-interventions (2 of 20 vs 0 of 20; $P = .468$), or readmissions (4 of 20 vs 1 of 20; $P = .339$), (Table III).

In the safety analysis, the complication rate in the MP group was 7 of 21 compared with 4 of 20 in the placebo group ($P = .484$). The patient with cardiac arrest was diagnosed with malignant hyperthermia and recovered fully. No adverse events related to the administration of MP were noted.

Discussion

In the current study, we found that a single, preoperative, high-dose administration of MP decreased both early pain and the inflammatory response in patients undergoing an AWR for large incisional hernia in a standardized enhanced recovery setting.

These results are in accordance with previous studies from other operative procedures, which reported improved analgesia after the administration of high-dose glucocorticoid.[5,9,15] We believe that this analgesic effect is likely owing to the anti-inflammatory response to glucocorticoid as reflected in the diminished postoperative levels of CRP.[4,16] The greatest decrease in CRP levels in the MP group was observed during the first 2 postoperative days, which correlated with the decrease in postoperative pain scores during the same time interval. In accordance with previous studies on colorectal, vascular, and orthopedic surgery, administration of MP led to a decrease in the early postoperative inflammatory response as reflected in CRP levels.[4,17,18] Contrary to studies on orthopedic surgery, we did not find any decrease in fatigue, nausea, or vomiting.[18,19] The operative trauma as part of the AWR results in a relative postoperative ileus, which hypothetically is less affected by the preoperatively administered MP. The lack of differences in postoperative nausea or fatigue between the 2 groups may be owing to insufficient statistical power[20] or may reflect no actual difference in the effects of MP during this operation.

Importantly, there were no differences between the groups in the rates of postoperative wound complications, operative re-interventions, or readmissions, and the 3 intraoperative, inadvertent enterotomies in the MP group cannot be considered related to the administration of MP. We want to acknowledge that our study had inadequate power to make any definite conclusions about safety issues concerning the use of a single high dose of MP. A large meta-analysis on the role of glucocorticoids in abdominal surgery reported that single-shot, preoperative administration of high-dose glucocorticoids leads to decreased rates of both complications overall and infectious complications.[6] In addition, a recent meta-analysis on non-cardiac surgery including 5,607 patients reported no safety issues related to the preoperative, single administration of a glucocorticoid.[7] In the current study, 1 patient was excluded, because he was unable to contribute to the primary outcome owing to postoperative cardiac arrest. We have no reason to believe that this was related to the preoperative, high-dose glucocorticoid treatment, however; a minor bias owing to this inclusion cannot be ruled out.

In contrast to several other similar studies across vascular, orthopedic, colorectal, and hepatobiliary surgery, we found no difference in postoperative duration of stay between the 2 groups.[4,20–22] All the included patients in the present randomized trial followed an enhanced perioperative recovery protocol, which is the standard postoperative care package for patients undergoing AWR at our institution.[23] Since the introduction of this

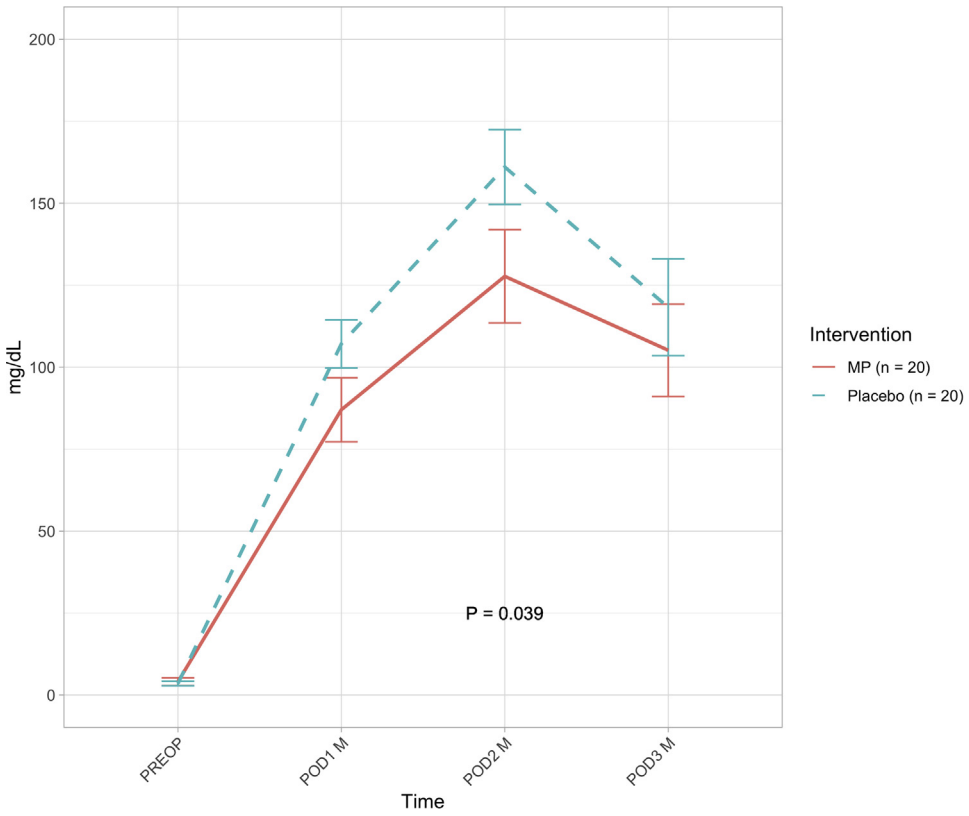

Fig 4. Mean CRP after abdominal wall reconstruction in patients preoperatively treated with either 125 mg MP or placebo. Bars indicate standard error of the means.

recovery protocol, the postoperative hospital stay after AWR has been decreased to a median of 4 days, thus representing a level where any further decrease may be unachievable with current methods of postoperative care.[24] Moreover, all patients had an epidural infusion of analgesics until the morning on postoperative day 3. Thus, patients, who might otherwise have been ready for discharge earlier than postoperative day 3, were not given this possibility, because the discharge criteria encompassed sufficient pain relief by oral analgesics only. In recent years, several publications have been published on the effects of enhanced recovery protocols after AWR, underlining the need for continuous research in this field.[3,24–26] The current study provides results for improvement of the recovery after AWR for large incisional hernias

Analgesic treatment of patients undergoing AWR has been subject to recent debate. A retrospective analysis from the Americas Hernia Society Quality Collaborative reported epidural analgesia to be associated with more pain, increased duration of stay, and a greater complication rate compared with no epidural analgesia in patients undergoing elective ventral hernia repair.[27] As an alternative to epidural analgesia, transversus abdominis plane block using a long-acting bupivacaine liposome suspension (Exparel; Pacira Pharmaceuticals Inc, San Diego, CA) is a promising novel treatment in patients undergoing AWR, although more data are required.[25] Future studies of analgesic treatment in AWR should focus on comparison of epidural and transversus abdominis plane blocks, though the findings of the present trial suggest that attenuation of the postoperative inflammatory response is beneficial even in patients already offered an intensive, perioperative prevention of pain.

In conclusion, a preoperative, single-shot, high-dose MP before AWR for a large incisional hernia appears to result in less early postoperative pain and an attenuated inflammatory response. Future studies should focus on the safety of MP administration in patients undergoing AWR.

Funding/Support

None.

Conflict of interest/Disclosures

None of the authors have any conflicts of interest.

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