Randomized Trial

The Dose-Dependent Effects of Ketoprofen on Dynamic Pain after Open Heart Surgery

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Background: Non-steroidal anti-inflammatory drugs (NSAIDs) can reduce postoperative pain, in both static (i.e., at rest) and dynamic contexts (e.g., during coughing or mobilization), and reduced doses could improve their efficacy/tolerance balance.

Objectives: To test this hypothesis of efficacy after open heart surgery, in which NSAIDs are poorly used, particularly for safety concerns.

Study Design: Randomized, double-blind trial.

Setting: Single-center, French university hospital.

Methods: Patients. One hundred patients at low risk of postoperative complications undergoing scheduled open heart surgery (97 analyzed). Intervention. We tested intravenous ketoprofen, at a dose of 0.5 mg/kg-1 every 6 hours during the 48 hours following the end of sedation, after surgery. This standard protocol was compared to a similar one in which half doses were administered, to one with quarter doses, as well as to a placebo group. Analgesia was supplemented by acetaminophen plus self- and nurse-administered intravenous morphine. Measurement. The primary outcome was the intensity of dynamic pain, assessed over 48 hours on an 11-point numerical rating scale (NRS).

Results: Only the full-dose ketoprofen group showed reduced dynamic and static postoperative pain vs. placebo ($P < 0.00001$ for both). The evolution of dynamic pain suggested a delayed and therefore non-significant effect with the low doses. Ketoprofen did not affect either the postoperative morphine consumption or the tolerance outcomes, such as the volumes of chest tube drainage and the renal function.

Limitations: This pilot trial was undersized to test major tolerance outcomes.

Conclusions: Although we failed to demonstrate any analgesic effects with low doses of ketoprofen, we confirmed the good efficacy/tolerance balance with this propionic NSAID of intermediate COX_2-selectivity. Lower doses of NSAIDs, potentiated by a loading dose, should be tested in the future.

IRB approval: CPP Sud-Est VI (Clermont-Ferrand, France), on 12/23/2013.
Clinical trial registry: EudraCT (2013-003878-27); ClinicalTrials.gov (NCT02180087).

Key words: Non-steroidal anti-inflammatory drugs, ketoprofen, cyclooxygenase, pain, postoperative, sternotomy, postoperative rehabilitation, analgesia, side effects

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Pain following sternotomy is moderate to severe (1,2), and the current multimodal analgesia has shown good efficacy for pain at rest, although the use of opioids can have side effects. However, "dynamic" pain, i.e., induced by the patient's movements or mobilization for nursing, which may impact postoperative rehabilitation (3), is more resistant to current analgesia (1,2,4),

and may require techniques such as locoregional anesthesia, which is controversial in cardiac surgery (5). Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown effective to relieve some aspects of dynamic pain in various surgeries (6-11), including sternotomy (12). They also have an opioid-sparing effect after cardiothoracic surgery (13). Nevertheless, the routine use of NSAIDs in cardiac surgery raises tolerance issues of various importance, from a general reluctance due to the gastric and renal side effects (14) to the clearly identified pro-thrombotic effects of COX2-selective NSAIDs (15,16). For these reasons, the US Food and Drug Administration discouraged the use of any NSAID in coronary surgery in 2005 (17), while, for example, the injectable non-selective NSAID ketoprofen – labelled for postoperative pain in France – does not exclude cardiac surgery (18). Also, there is a need to consider the interest of administering lower doses of NSAIDs, under the hypothesis that the analgesic efficacy would not be affected (19-21), while side effects would be reduced (22). The aim of this pilot trial is to test the efficacy hypothesis, with postoperative dynamic pain as a primary outcome. Studying tolerance – through intermediate outcomes – was a secondary endpoint.

Methods

This prospective randomized, placebo-controlled, double-blind, single-center trial was approved by the referent research ethics committee and registered on Clinical-Trials.gov (NCT02180087) and EudraCT (2013-003878-27). The inclusion criteria were adult patients, aged 18 to 75, with a body weight from 60 to 100 kg, scheduled for open heart surgery with sternotomy for valve replacement or coronary artery bypass grafting (CABG), with cardiopulmonary bypass (CPB). The exclusion criteria were renal insufficiency defined as a creatinine clearance < 60 mL/min^{-1} (estimated by the Modification of Diet in Renal Disease study equation for a 1.73-m^2 body surface), hepatic insufficiency, congestive heart failure with ejection fraction < 45%, history of gastric peptic ulcer or gastrointestinal bleeding (≥ 2 distinct episodes of bleeding), diabetes mellitus needing insulin therapy, preoperative coagulation disorder, allergy to NSAID, pregnancy or breastfeeding, incapacity to understand the protocol and sign the consent or use patient-controlled analgesia (PCA), emergency surgery, heart transplant, aortic dissection, additional thoracotomy, and redo sternotomy. Patients received a detailed explanation of the study during a preoperative consultation. The day before surgery, they gave their signed consent, were shown how to report pain on an 11-point numerical rating scale (NRS) from 0 (no pain) to 10 (maximum pain), and how to use the PCA device. The upper limit for weight was defined in order to keep in the recommended dose range, and the lower limit, to fit to the study population (mean weight estimated at 79 kg from pilot data).

Patients were premedicated with hydroxyzine. General anesthesia was conducted under a standard monitoring with invasive blood pressure, 5-lead electrocardiography, bispectral index monitor, pulse-oximetry, neuromuscular monitoring, 4-port central jugular venous line, and urinary catheter. Induction of anesthesia was conducted with intravenous (i.v.) propofol, sufentanil, and cisatracurium; after tracheal intubation, anesthesia was maintained with the same drugs by continuous infusion, except before and after CPB, during which hypnosis was achieved by inhaled sevoflurane. The target for bispectral index was 40 – 60. Sufentanil was started at 0.5 $\mu g/kg/hr^{-1}$, then modulated according to clinical observation. The mechanical ventilation targeted a $PETCO_2$ in the 30 – 35 mmHg range, and SpO_2 over 95%. Antibiotic prophylaxis was achieved by cefuroxime (for 48 hours) and prevention of bleeding by tranexamic acid. At CPB withdrawal, hemodynamics were controlled using, if necessary, the temporary tilt position, intravascular fluid loading, cardiac electrical pacing, and vasoactive or inotropic support.

Patients were randomized into one of the 4 study groups. In the group "ketoprofen full dose" (Kfull) group, the patients received intravenous ketoprofen (Kétoprofène Medac®, Lyon, France, presented in 4-mL/100-mg ampoule), 0.5 $mg.kg^{-1}$ every 6 hours until the forty-eighth postoperative hour. In the "ketoprofen half dose" (K½d) and the "ketoprofen quarter dose" (K¼d), the protocol was the same, but the respective doses of ketoprofen administered at each time were 0.25 and 0.125 $mg.kg^{-1}$. In the placebo group, only normal saline was administered. The study drug was prepared by an anesthetist nurse not involved of postoperative care, under the control of the anesthetist in charge of the patient, who opened the allocation envelope. For each patient, the study solution was prepared in a sterile manner for the following 48 hours (one vial for each 24 hours). Respectively for the Kfull, K½d, K¼d and placebo groups, 8, 4, 2, or 0 mL of ketoprofen (100 mg/mL^{-1}) were diluted in 20 mL normal saline in a syringe. A weight-defined volume of this 20 mL corresponding to the target dose for 24 hours was then

kept (e.g., for 80 kg, 16 mL = 160, 80, 40, or 0 mg per 24 hours). This daily dose was diluted in a vial of normal saline to a final volume of 120 mL. The vial was protected from daylight and 30 mL were transferred every 6 hours via a closed line to an electrically-driven syringe for a 30-minute infusion. This procedure was in accordance with the stability data for the drug. The treatment was started just before the sedation was discontinued, i.e., before the patient woke up in the postoperative care unit (PACU); this was defined as T0. All providers were blinded to the treatment group, and the patient was unaware of the treatment administered throughout the study. Nobody in the PACU and surgical ward staff was aware of the treatment administered.

Sedation was maintained with intravenously administered propofol during transport from the operating room, then until tracheal extubation. Mechanical ventilation in the PACU was maintained with the same parameters. Routine intensive care monitoring, chest radiography, and electrocardiography were performed as well as standard laboratory tests at T0, then daily and at the physician's request. Sedation was discontinued when the patient's vital parameters and core temperature had returned to normal. The trachea was extubated once the patient could respond to simple commands and breathe spontaneously with good hematosis. All patients were placed in a 30-degree sitting position, a protocol for analgesia was applied with i.v. acetaminophen (1 g q6h), plus i.v. morphine chlorhydrate ad libitum (Morphine Aguettant, Lyon, F). Morphine was initiated by the referent nurse when the patient first requested it; 3 mg intravenously per bolus was administered until the pain score went under 3/10, then it was delivered via a PCA device (Frydom 5, Vygon, Ecouen, F). The protocol for PCA included dilution into normal saline of morphine (1 mg/mL^{-1}) plus droperidol (0.05 mg/mL^{-1}), 1-mL boluses, and a 7-minute refractory period, with no continuous infusion. The standard postcardiac surgery care included preventive anticoagulation by i.v. heparin followed by oral aspirin. Medications were given orally at POD1 if possible, with priority to the cardiovascular-targeting ones. The patient was transferred to the surgical ward when none of the following was necessary: inotropic or vasopressive treatment, mechanical ventilation, or dialysis, and in the absence of a life-threatening rhythm disturbance.

The primary outcome was the intensity (NRS) of dynamic pain, measured as the mean of the pain scores evoked by coughing, horizontal placement of the patient to measure the central venous pressure measurement, and sideways turning of the patient for nursing. The secondary efficacy outcomes were intensity of pain during movement, considering each condition separately; intensity of pain at rest at different sites (sternotomy, back, and site of saphenous vein harvesting if any); postoperative morphine consumption; sedation as quoted on the Ramsay's scale; postoperative recovery parameters (flatus, dietary intake, and oral medication intake); and global satisfaction of the patient recorded on a 5-point Likert-like scale (0 = not satisfied at all; 1 = unsatisfied; 2 = somewhat satisfied; 3 = satisfied; 4 = very satisfied). The secondary tolerance outcomes were blood gas analyses; chest drain product and removal time; occurrence of postoperative nausea and vomiting; report of postoperative complications; and length of stay in the PACU. The following events were considered as relevant complications: acute renal failure according to the Kidney Disease, Improving Global Outcome (KDIGO) criteria based on urinary output per 4 hours, serum creatinine level at POD1 and POD2, and creatinine clearance at POD2 (23); need for mechanical ventilation over 24 hours; pneumonia; myocardial infarction; cardiac arrhythmia de novo needing medication or cardioversion; acute pulmonary edema; stroke; coma, mediastinal or sternal wound infection, bleeding in chest drains > 50 mL/hr^{-1} or bleeding needing reoperation, gastric or intestinal hemorrhage, and any need for readmission in PACU within the 2 weeks after surgery. The outcomes were recorded from the first administration of the study drug at T0, then every 4 hours until T0+48 hours.

Analyses were performed using Stata 13. The tests were 2-sided, with α = 0.05. Quantitative data were expressed as mean ± SD for a normal distribution and otherwise as quartiles. The normality of the distribution was checked with a Shapiro-Wilk test. Comparisons between groups for non-repeated data were conducted using, for categorical variables, Chi-squared or Fisher exact tests, and for quantitative parameters, either an ANOVA for a normal distribution with homoscedasticity, otherwise a Kruskall-Wallis test. For comparison of pain scores between the 2 groups, the raw data were analyzed without replacing the missing data. In addition, at each observation time, composite scores for pain at rest (static) and during mobilization (dynamic) were generated. Static pain was the average of sternal and dorsal pain at rest; dynamic pain was the average of pain during coughing, measurement of CVP, and nursing care. Missing data were replaced using the formula from a linear regression based on the full set

of observations, first within each domain of pain (static/dynamic), then – if all data were missing for one domain – information was taken from the other domain. This approach was chosen to improve the estimation of the effect size for each domain of pain. Repeated longitudinal data were analyzed using random-effect regression models (group, time-point evaluation, and their interaction as fixed effects) taking into account between- and within-patient variability (subject as random-effect). The normality of residuals was checked.

We worked on the hypothesis of there being a significant reduction of pain in one of the ketoprofen groups vs. the placebo group. The sample size was estimated from data obtained in a pilot open non-randomized study comparing administration of ketoprofen 50 mg q6h to none administered. The mean differences (in mm out of 100, ± SD) for pain at rest, pain during central venous pressure measurement, and pain during nursing were 13 ± 10, 22 ± 17 and 29 ± 19, respectively. With $\alpha = 0.05/6$ and $1-\alpha = 0.95$, the group size was 22, 22, and 16. We reset it to 25 to consider secondary exclusions.

Results

The study started on 01/31/2014. The flow chart for the trial is shown in Fig. 1. Table 1 shows the characteristics of the 4 groups before randomization, showing a good homogeneity between groups, except for gender, as there was an overrepresentation of women in the placebo group.

Table 2 shows the effects of the studied treatment on outcomes related to the analgesic efficacy, either directly or indirectly, i.e., through an eventual improvement in respiratory function or a reduction of opioid-induced side effects. For both pain at rest and dynamic pain, the linear mixed model was found to be significant, while the post hoc analyses (Tukey-Kramer's test) showed that only the Kfull group differed from the placebo group. Besides, no difference was found for any of the analgesia-related secondary outcomes, except for vomiting, which was more frequent in the placebo group compared to the 3 ketoprofen groups. Also, a non-significant trend for greater patient satisfaction with the analgesia appeared in the ketoprofen groups.

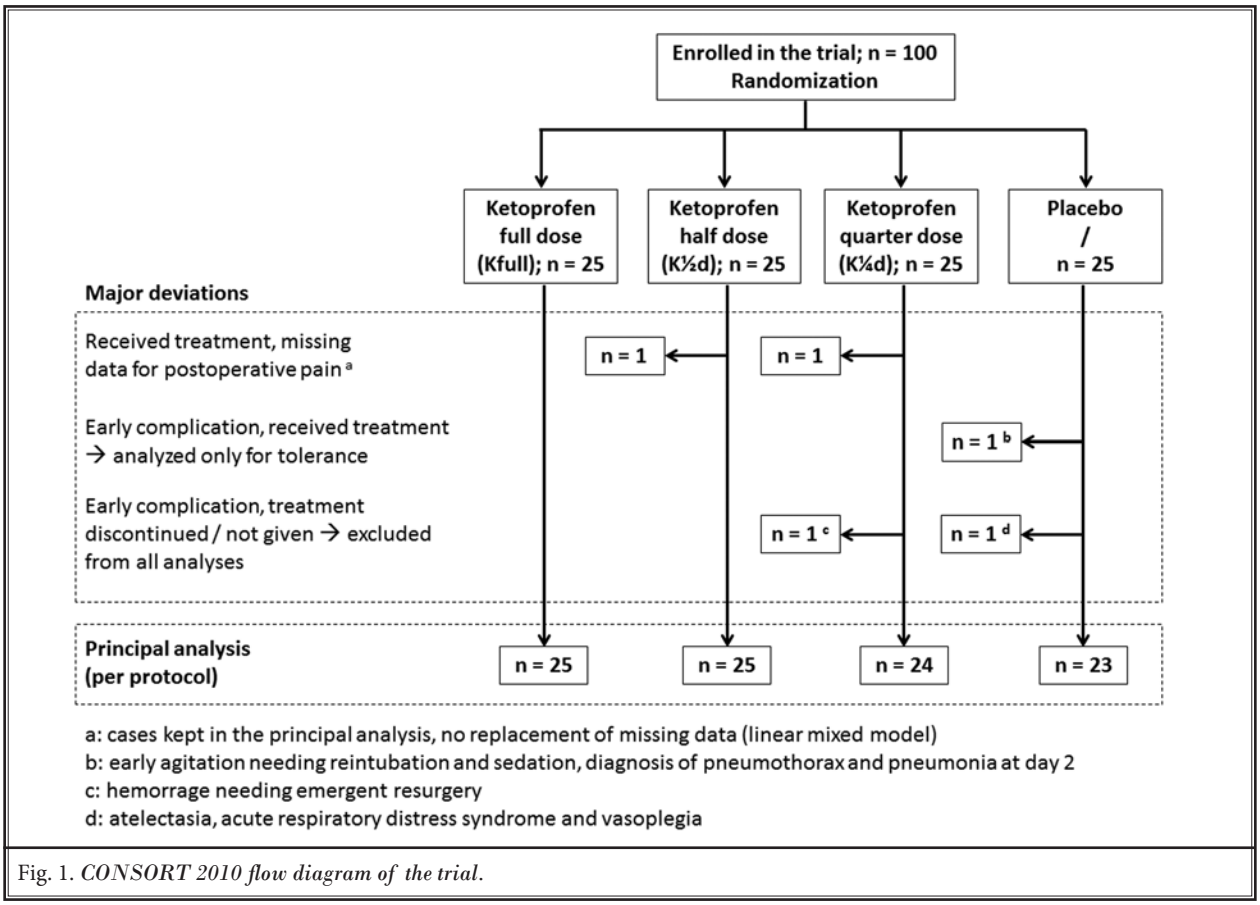

Fig. 1. *CONSORT 2010 flow diagram of the trial.*

Table 1. *Baseline characteristics*.

	Placebo (n = 24)	K¼d (n = 24)	K½d (n = 25)	Kfull (n = 25)	*P* value
Preoperative characteristics					
Age (years)	58 ± 13	60 ± 11	63 ± 7	63 ± 9	0.501
Height (cm)	170 ± 8	173 ± 6	170 ± 7	172 ± 8	0.362
Weight (kg)	77 ± 8	80 ± 10	80 ± 9	79 ± 9	0.629
Body mass index (kg/m-2)	27 ± 2	27 ± 2	28 ± 3	27 ± 3	0.703
Gender: females	11 (45.8)	0 (0.0)	3 (12.0)	2 (8.0)	< 0.001
Euroscore 2 (%)	1.1 [0.9 – 1.7]	1 [1 – 1]	1 [0.8 – 1.6]	1.4 [0.9 – 2.5]	0.288
Uremia (mmol/L^{-1})	5.8 ± 1.4	6.1 ± 1.4	5.8 ± 1.3	5.9 ± 1.4	0.874
Creatininemia (µmol/L^{-1})	75 ± 16	86 ± 10	82 ± 16	82 ± 13	0.095
Creatinine clearance (mL/min^{-1}/1.73m^2)[a]	86 [76 – 99]	80 [74 – 90]	79 [70 – 103]	79 [70 – 104]	0.942
Arteritis (all sites)	11 (47.8)	9 (37.5)	15 (60.0)	15 (60.0)	0.305
Arterial hypertension	9 (37.5)	9 (37.5)	8 (32.0)	12 (48.0)	0.703
Atrial fibrillation / flutter	0 (0.0)	3 (12.5)	3 (12.0)	4 (16.0)	0.237
Pulmonary arterial hypertension	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0.490
History of thromboembolic event	0 (0.0)	0 (0.0)	1 (4.0)	1 (4.0)	1.000
Chronic obstructive pulmonary disease	3 (12.5)	3 (12.5)	4 (16.0)	4 (16.0)	1.000
Dyspnea	5 (20.8)	11 (45.8)	6 (24.0)	9 (36.0)	0.219
Sleep apnea syndrome	0 (0.0)	0 (0.0)	2 (8.0)	3 (12.0)	0.163
History of stroke	1 (4.2)	0 (0.0)	1 (4.0)	2 (8.0)	0.900
Mental disease / alcoholism	2 (8.3)	1 (4.2)	2 (8.0)	1 (4.0)	0.951
Diabetes	3 (12.5)	1 (4.2)	2 (8.0)	2 (8.0)	0.785
Dyslipidemia	4 (16.7)	5 (20.8)	5 (20.0)	6 (24.0)	0.938
Thyroid disease	2 (8.3)	0 (0.0)	1 (4.0)	0 (0.0)	0.325
History of cancer	1 (4.2)	1 (4.2)	3 (12.0)	2 (8.0)	0.831
Surgery and anesthesia					
Total duration of surgery (min)	238 ± 72	221 ± 69	208 ± 75	211 ± 63	0.462
Duration of extracorporeal circulation (min)	92 [75 – 109]	89 [68 – 109]	80 [75 – 100]	82 [60 – 91]	0.432
Dose of intraoperative sufentanil (µg)	155 [129 – 191]	145 [126 – 196]	147 [121 – 170]	145 [125 – 175]	0.967
Valve repair / replacement	16 (66.7)	17 (70.8)	15 (60.0)	12 (48.0)	0.401
Aortic	11	13	11	10	
Mitral	4	4	4	2	
Tricuspid	3	0	2	0	
Coronary bypass / type of graft	9 (37.5)	8 (33.3)	13 (52.0)	15 (60.0)	0.205
Left internal thoracic artery	9	7	13	15	NC
Right internal thoracic artery	7	4	11	12	
Saphenous	5	4	9	8	
No. of anastomoses (when applicable)					
1	1	2	0	1	NC
2	1	3	2	3	
3	4	2	7	6	
4 - 6	3	1	4	5	
Delay between admission in PACU and H0 (hrs)	4.7 [4 – 6.2]	5.2 [2.9 – 6.1]	5 [4 – 6]	4.7 [4 – 6.2]	0.953

Initial characteristics of the patients, according to the group of randomization; Kfull, K½d, and K¼d for ketoprofen full dose, half dose, and quarter dose, i.e., 0.5, 0.25, and 0.125 mg/kg-1 every 6 hours until the forty-eighth postoperative hour, respectively. Numerical data are expressed as mean ± SD or median [interquartile range]. Categorical data are expressed as number of patients and (%). H0 is the time of initiation of the treatment, i.e., one hour before the planned time for discontinuation of sedation. Abbreviations; NC: not calculated. Notes; [a] estimated according to the Modification of Diet in Renal Disease (MDRD).

Table 2. *Efficacy outcomes*.

	Placebo (n = 23)	K¼d (n = 24)	K½d (n = 25)	Kfull (n = 25)	*P* value
Pain and analgesia					
Postoperative pain at rest a	1.9 ± 1.2	1.6 ± 1.2	1.3 ± 0.9	1.2 ± 0.6	< 0.00001
Dynamic postoperative pain[a]	3.6 ± 1.4	3.3 ± 1.5	3.2 ± 1.2	2.6 ± 1.2	< 0.00001
Morphine consumption (mg)[b]	32 [20.5 – 51.5]	28.5 [17 – 41.5]	25 [18 – 55]	38 [27 – 45]	0.524
Need for rescue analgesia	4 (17.4)	3 (12.5)	3 (12.0)	3 (12.0)	0.825
Patient's satisfaction with analgesia: good / very good[c]	16 (69.6)	19 (82.6)	21 (87.5)	21 (84.0)	0.487
Respiratory outcomes					
Averaged respiratory rate (min^{-1})	17.3 [16.4 – 19.2]	18.4 [16.5 – 20.0]	17.5 [16.3 – 19.0]	17 [15.6 – 17.9]	0.219
No. of hypoxemic events ($SpO_2 \leq 92\%$)	1 [0 – 1]	0.5 [0 – 1]	0 [0 – 1]	0 [0 – 1]	0.225
Averaged PaO_2 / FIO_2 (mmHg)	292 ± 131	301 ± 80	282 ± 99	294 ± 91	0.937
No. of hypoxemic events (on blood gases)[d]	2 [1 – 4]	1 [0 – 2]	3 [0 – 5]	2 [1 – 4]	0.419
Averaged $PaCO_2$ (mmHg)	38.7 ± 3.1	38.8 ± 3.6	37.2 ± 3.2	38.7 ± 3.1	0.342
No. of hypoventilation events (on blood gases)[e]	0 [0 – 0]	0 [0 – 1]	0 [0 – 0]	0 [0 – 0]	0.270
Time from H0 spent under oxygen (hrs)	68 [58 – 105]	48 [45 – 73]	90 [48 – 137]	72 [56 – 113]	0.086
Other outcomes					
Nausea	5 (21.7)	4 (16.7)	6 (24.0)	4 (16.0)	0.879
Vomiting	5 (21.7)	1 (4.2)	0 (0.0)	1 (4.0)	0.017
Delay since H0 to the first event (hrs)					
Flatus	36 [28 – 46]	32 [24 – 45]	32 [24 – 40]	32 [24 – 48]	0.672
Feces	52 [52 – 52]	52 [52 – 52]	52 [52 – 52]	52 [52 – 52]	0.636
Oral medication intake	24 [20 – 32]	24 [23 – 30]	28 [20 – 32]	24 [20 – 32]	0.805
First sitting	45 [41 – 49]	47 [44 – 51]	47 [42 – 51]	46 [43 – 49]	0.717
Discharge from ICU	32 [21 – 68]	26 [22 – 45]	44 [23 – 70]	43 [22 – 45]	0.371

Initial characteristics of the patients, according to the group of randomization; Kfull, K½d, and K¼d for ketoprofen full dose, half dose, and quarter dose, i.e., 0.5, 0.25, and 0.125 mg/kg^{-1} every 6 hours until the forty-eighth postoperative hour, respectively. Numerical data are expressed as mean ± SD or median [interquartile range]. Categorical data are expressed as number of patients and (%). H0 is the time of initiation of the treatment, i.e., one hour before the planned time for discontinuation of sedation. Abbreviations; ICU: intensive care unit; NA: not applicable. Notes; [a] the displayed data are the grand means calculated from all the measurements from H0+4 hours to H0+48 hours, and the *P* value relates to the linear mixed model; [b] during the first 48 postoperative hours; [c] missing data for one patient in the K¼d group and one in the K½d group; [d] defined as PaO_2 / FIO_2 < 300 mmHg; [e] defined as $PaCO_2$ > 45 mmHg.

Due to the unexpected imbalance (see above), we conducted an additional analysis of both pain at rest and dynamic pain adjusted to gender, which showed similar *P* values for the whole model, while a difference from the placebo group was found, not only for the Kfull, but also for the K½d group. In addition, to check that the patients of the placebo group did not behave differently due to the higher rate of women, we extracted data from an additional observational cohort of 20 male patients with the same entry criteria as those of the main study. Respectively for postoperative pain at rest, dynamic postoperative pain, and morphine consumption, neither the raw values (1.7/10 ± 1.2; 3.6/10 ± 1.4; 42 mg ± 17), nor the coefficients of variation (overlapping of the confidence intervals) differed from the placebo group.

For descriptive purposes only, the time course of pain intensity tended to decrease with time, in both conditions (Fig. 2). Pain intensity at rest was generally low (i.e., < 3/10), as expected according to the protocol; the intensity of dynamic pain was higher. In both conditions, the effect of the full dose of ketoprofen (Kfull, the only one being significant) appeared for the early measurements, while it faded for the very late observations. With the lower doses of ketoprofen, a mild effect was observed, but not for the early measurements.

Table 3 shows that tolerance was similar for all 3 doses of ketoprofen compared to the placebo, espe-

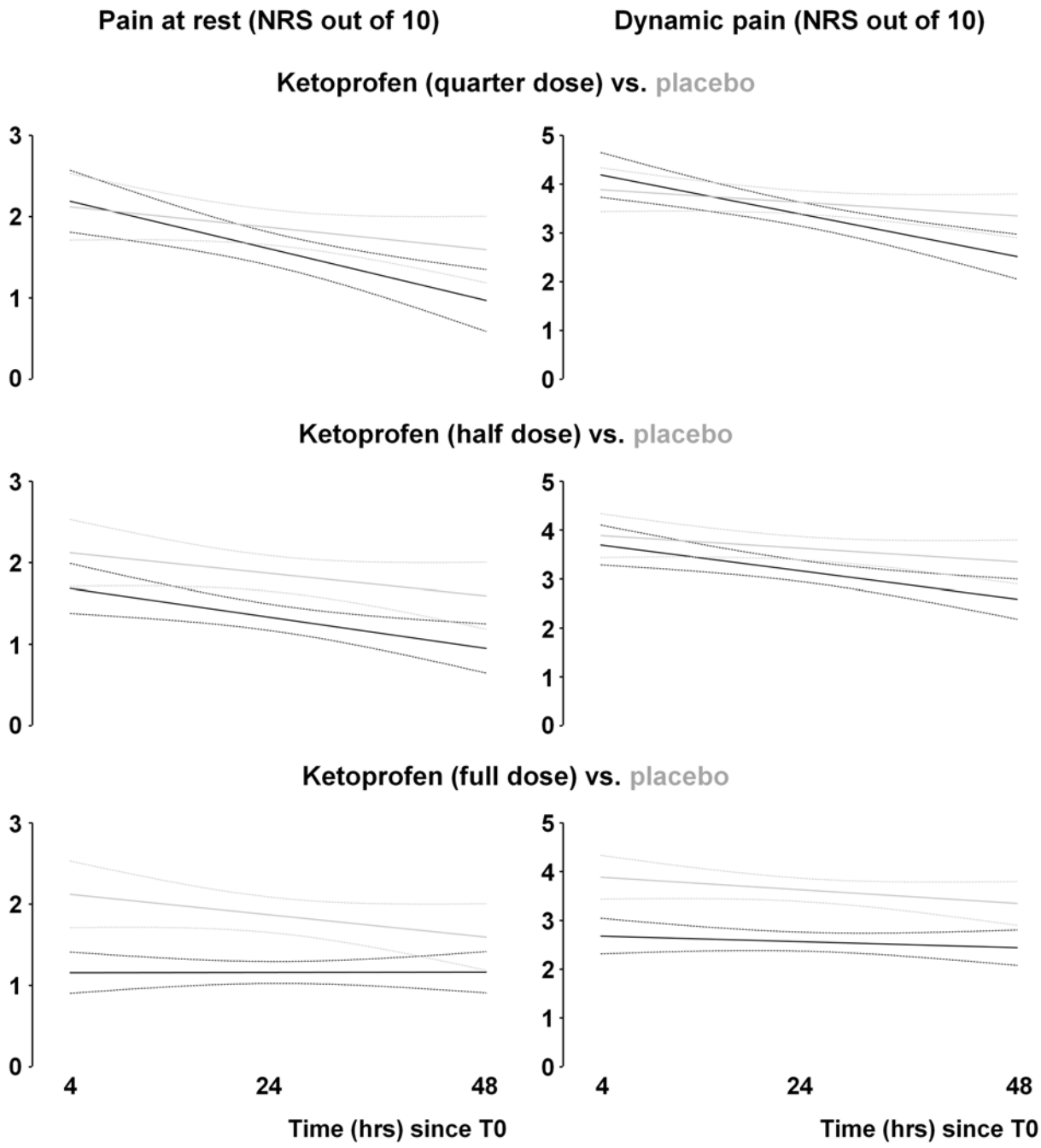

Fig. 2. *Time course of pain intensity at rest (left) and of dynamic pain (right, see Methods for calculation). The linear regression curve of the pain scores plotted against the time since treatment initiation ("T0," i.e., just before discontinuation of sedation) is displayed with its 95% confidence interval limits. Each ketoprofen group is compared to the placebo (black vs. gray lines). The full dose of ketoprofen corresponds to 0.5 mg/kg-1 every 6 hours, from T0 and over a period of 48 hours. Note that the scales for the y axes (pain intensity) are not the same as for pain at rest and dynamic pain.*

cially for the chest tube drainage production and renal function. There was a general improvement in renal function from preoperative values at the forty-eighth postoperative hour, which was most marked in the Kfull group.

Discussion

The current study confirmed the analgesic properties of the NSAID ketoprofen after open heart surgery (on both static and dynamic pain), with no apparent increase in side effects. However, reducing the doses to half or quarter of the full recommended dose did not significantly reduce the pain outcomes in comparison to those of the placebo. Only the post hoc analysis adjusted for gender showed an effect of the half dose. Similar effects of NSAIDs have already been documented in the past, although the information was incomplete. A meta-analysis in 2006 suggested that NSAIDs reduced pain and morphine consumption after cardiothoracic surgery, but cardiac surgery was poorly represented, molecules and protocols were heterogeneous, and the pooled magnitude of effect was small (13). In those studies conducted in cardiac surgery, the NSAID-induced analgesia was generally superior to control or placebo; none of them tested ketoprofen (12,15,24-27). Conversely, negative results were reported with ketoprofen (100 mg intrarectally once) and indomethacin (26,28). A key for efficacy seems to be a repeated administration of the NSAID. In a double-blind trial vs. placebo, naproxen (administered intrarectally then orally, until day 5) reduced dynamic pain and better preserved the patients' slow vital capacity (12). The mean difference on pain intensity after physiotherapy was 1.9 out of 10, vs. 1.0 in the current study. Also, in both studies, the opioid consumption was unaffected; this could be due to a low statistical power, the concomitant use acetaminophen, or resistance of dynamic pain to opioids.

NSAIDs probably induce analgesia through an inhibition of prostaglandin synthesis (29). A peripheral action – consistent with an effect on dynamic pain – is supported by human data, as ibuprofen inhibits the production of cytokines in inflamed skin in healthy volunteers (30), and injection of diclofenac or ketorolac into the wound after a caesarean section has analgesic effects per se (31,32), together with a local anti-inflammatory action (32). A reduction in spinal sensitization is supported by preclinical data (33), while in healthy volunteers, parecoxib impairs the nociceptive flexion reflex, but not the wind-up, which signals central sensitization (34). Also, while intrathecal ketorolac reduces induced skin hypersensitivity in healthy volunteers (35), it did not have analgesic effects after vaginal hysterectomy (36).

The supporting hypothesis for the effectiveness of low doses is also heterogeneous. In the rat model of plantar incision, the analgesic effects of subcutaneous ketoprofen on guarding pain behavior or mechanical withdrawal threshold were quite similar with doses of 10 and 5 mg/kg^{-1} (37), while 10 mg/kg^{-1} was effective to blunt mechanical allodynia in a similar study (38); moreover, milder analgesic effects were observed at much lower doses (37). The recommended dose of ketoprofen for postoperative analgesia is 100 – 300 mg per 24 hours (18); the French current practice is to administer 50 mg every 6 hours; this based on a 2 hour-elimination half-life (39). A study conducted after general surgery showed that analgesia was obtained with 50 mg of oral ketoprofen, the effects of 150 mg were no better, and 25 mg also had analgesic effects, although shorter-lived (40). A meta-analysis confirmed this range of effective doses, although most of the studies included minor surgeries (20). After minor surgery, the ED50 of ketoprofen has been estimated at 30 mg (41). In ambulatory emergency patients with bone and joint pain, a daily dose of 200 mg of ketoprofen was found equivalent to 300 mg (21). Finally, a study of ketorolac administered every 6 hours after spine stabilization showed that morphine consumption was reduced from doses of 7.5 mg, and that a ceiling effect was reached with 12.5 mg, while the currently prescribed dose was 10 – 30 mg (19). The current study confirmed that a reduction of dynamic pain after major surgery could be obtained with moderate doses of ketoprofen (0.5 mg/kg^{-1} corresponds to 40 mg for an 80-kg weight). The failure of the half dose could be explained by the desired strength of the studied outcome, but the time path of the effect also suggests that some efficacy could be obtained with doses of 0.25 mg/kg^{-1} if a loading dose was administered initially.

Although statistical power was insufficient to identify differences in tolerance outcomes, our results do not militate against the use of ketoprofen after open heart surgery. However, only a large trial focusing on tolerance could influence the practice, while the 2005 FDA advisory had sensibly decreased the use of NSAIDs after CABG (42,43). Concerning the potential nephrotoxicity of NSAIDs after an already risky procedure (44), the data from the literature are more optimistic (42,45). Generally, no increased renal impairment was found for

Table 3. *Tolerance outcomes*.

	Placebo (n = 24)	K¼d (n = 24)	K½d (n = 25)	Kfull (n = 25)	*P* value
Chest tube drainage					
Pericardial tubes, total volume (mL)	155 [95 – 205]	195 [143 – 250]	156 [100 – 240]	200 [100 – 248]	0.549
Retrosternal tubes, total volume (mL)	150 [115 – 200]	143 [100 – 260]	180 [100 – 220]	210 [160 – 250]	0.167
All mediastinal chest tubes, total volume (mL)	314 [235 – 403]	365 [288 – 463]	310 [255 – 460]	400 [290 – 618]	0.240
Time to withdrawal of mediastinal chest tubes (hrs)	69 [45 – 89]	66 [45 – 71]	54 [45 – 69]	68 [44 – 90]	0.699
All chest tubes including pleural, total volume (mL)	563 [260 – 700]	415 [322 – 580]	570 [318 – 820]	650 [475 – 800]	0.357
Renal function					
Urinary output of the first 48 postoperative hours (L)	3.31 [2.67 – 4.06]	3.14 [2.65 – 4.07]	3.24 [2.55 – 4.41]	3.57 [2.54 – 3.86]	0.023
Drop in creatininemia (% of preoperative)	18 [8 – 23]	16 [9 – 23]	18 [13 – 25]	9 [7 – 21]	0.306
Gain in creatinine clearance (% of preoperative)[a]	26 ± 29	28 ± 23	31 ± 32	17 ± 22	0.035
Drop in uremia (% of preoperative)	24 [12 – 44]	31 [14 – 46]	28 [6 – 38]	19 [5 – 30]	0.317
Delayed acute renal insuffiency	3 (12.5)	4 (16.7)	3 (12.0)	3 (12.0)	0.956
General events					
Readmission to ICU	1 (4.2)	0 (0.0)	1 (4.0)	0 (0.0)	0.869
In-hospital death[b]	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)	1.000
Declared adverse event	6 (25.0)	7 (28.0)	7 (29.2)	5 (20.0)	0.884
Declared serious adverse event	1 (4.2)	0 (0.0)	2 (8.0)	0 (0.0)	0.515
Cardiac events					
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Low cardiac output	1 (4.2)	0 (0.0)	1 (4.0)	0 (0.0)	0.869
Cardiac arrhythmia (supraventricular)	2 (8.3)	2 (8.3)	6 (24.0)	2 (8.0)	0.308
Need for pacemaker implantation	1 (4.2)	1 (4.2)	0 (0.0)	0 (0.0)	0.364
Cardiac tamponade	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Infectious events					
Temperature > 38°C	5 (20.8)	5 (20.8)	8 (32.0)	5 (20.0)	0.730
Mechanical ventilation exceeding 24 hrs	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0.490
Pneumonia[c]	2 (8.3)	1 (4.2)	0 (0.0)	0 (0.0)	0.270
Wound infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.0)	0.242
Infection other than wound/sternal	3 (12.0)	1 (4.2)	1 (4.0)	1 (4.0)	0.654
Sternal complication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Neurological events					
Delirium / mental confusion	1 (4.2)	1 (4.2)	0 (0.0)	0 (0.0)	0.364
Stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Other events					
Prolonged ileus	6 (25.0)	5 (20.8)	4 (16.0)	5 (20.0)	0.888
Other digestive complication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Trouble involving hemostasis	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)	1.000

Initial characteristics of the patients, according to the randomization groups; Kfull, K½d and K¼d for ketoprofen "full dose", "half dose" and "quarter dose", i.e. 0.5, 0.25 and 0.125 $mg.kg^{-1}$ every 6 hrs until the 48th postoperative hour, respectively. Numerical data are expressed as mean ± SD or median [interquartile range]. Categorical data are expressed as number of patients and (%). Abbreviations; ICU: intensive care unit. Notes; [a]estimated according to the Modification of Diet in Renal Disease (MDRD); [b]one sudden death case occurred on the 18th postoperative day, a heart block was suspected; [c]defined according to the Melbourne Group Scale, i.e. at least four of the following events = atelectasis or infiltration on chest X-ray, purulent sputum, physician diagnosis of pneumonia/chest infection, temperature > 38°C, SpO_2 < 90% on air, positive signs on sputum microbiology, white cell count > 11.2 units, or readmission/prolonged stay in ICU.

the NSAID groups, as long as the patients at risk had been previously excluded, and that doses and treatment duration were kept at a low range (13,44,46). Nevertheless, one large trial showed that coxibs increased the incidence of oliguria and renal dysfunction, but this could have been an indirect effect of other life-threatening complications due to the COX_2-selective NSAIDs (coxibs) (16). A strict selection also explains why the risk of gastric complication was not increased by NSAIDs, both in the previous studies (13) and the current one. The effects on hemostasis are highly dependent on the COX-selectivity (22): coxibs increase the risk of thrombotic events after CABG (16), and therefore have been banned for this purpose (17); in contrast, ketorolac or flurbiprofen, the most COX_1-selective, increase the risk of postoperative hemorrhage (47,48). After sternotomy however, in most of the trials which studied the effects of non-COX_2-selective NSAIDs on chest tube drainage (or equivalent), only one trial reported higher chest tube drainage during the early postoperative hours (12), this with naproxen which is less COX_1-selective than ketoprofen (22). Three other trials showed no difference (25,26,28).

The use of NSAIDs after cardiac surgery needs more rationale. There are arguments for a good efficacy/tolerance ratio for the NSAIDs with intermediate COX_2-selectivity (such as propionic agents), which are reinforced by our results. Nevertheless, this is restricted to selected patients, and no evidence exists for more fragile (e.g., older) patients. In the interests of treating these patients at risk, it would be interesting to retest lower doses of ketoprofen, but potentiated by a loading dose. The apparently good tolerance remains to be validated by a large trial.

Author Contributions:

Drs Vedat Eljezi (principal investigator), Bruno Pereira, and Christian Dualé had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All the authors designed the study protocol. Drs Vedat Eljezi (principal investigator) and Christian Dualé managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. All the authors provided revision for intellectual content and final approval of the manuscript.

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References

1. Milgrom LB, Brooks JA, Qi R, Bunnell K, Wuestfeld S, Beckman D. Pain levels experienced with activities after cardiac surgery. *Am J Crit Care* 2004; 13:116-125.
2. Lahtinen P, Kokki H, Hynynen M. Pain after cardiac surgery: A prospective cohort study of 1-year incidence and intensity. *Anesthesiology* 2006; 105:794-800.
3. Srikandarajah S, Gilron I. Systematic review of movement-evoked pain versus pain at rest in postsurgical clinical trials and meta-analyses: A fundamental distinction requiring standardized measurement. *Pain* 2011; 152:1734-1739.
4. Eljezi V, Dualé C, Azarnoush K, Skrzypczak Y, Sautou V, Pereira B, Tsokanis I, Schoeffler P. The analgesic effects of a bilateral sternal infusion of ropivacaine after cardiac surgery. *Reg Anesth Pain Med* 2012; 37:166-174.
5. Mazzeffi M, Khelemsky Y. Poststernotomy pain: A clinical review. *J Cardiothorac Vasc Anesth* 2011; 25:1163-1178.
6. Fletcher D, Zetlaoui P, Monin S, Bombart M, Samii K. Influence of timing on the analgesic effect of intravenous ketorolac after orthopedic surgery. *Pain* 1995; 61:291-297.
7. Picard P, Bazin JE, Conio N, Ruiz F, Schoeffler P. Ketorolac potentiates morphine in postoperative patient-controlled analgesia. *Pain* 1997; 73:401-406.
8. Singh H, Bossard RF, White PF, Yeatts RW. Effects of ketorolac versus bupivacaine coadministration during patient-controlled hydromorphone epidural analgesia after thoracotomy procedures. *Anesth Analg* 1997; 84:564-569.
9. Sinatra RS, Shen QJ, Halaszynski T, Luther MA, Shaheen Y. Preoperative rofecoxib oral suspension as an analgesic adjunct after lower abdominal surgery: The effects on effort-dependent pain and pulmonary function. *Anesth Analg* 2004; 98:135-140.
10. Martinez V, Belbachir A, Jaber A, Cherif K, Jamal A, Ozier Y, Sessler DI, Chauvin M, Fletcher D. The influence of timing of administration on the analgesic efficacy of parecoxib in orthopedic surgery. *Anesth Analg* 2007; 104:1521-1527.
11. Hojer Karlsen AP, Geisler A, Petersen PL, Mathiesen O, Dahl JB. Postoperative pain treatment after total hip arthroplasty: A systematic review. *Pain* 2015; 156:8-30.
12. Kulik A, Ruel M, Bourke ME, Sawyer L, Penning J, Nathan HJ, Mesana TG, Bedard P. Postoperative naproxen after coronary artery bypass surgery: A double-blind randomized controlled trial. *Eur J Cardiothorac Surg* 2004; 26:694-700.
13. Bainbridge D, Cheng DC, Martin JE, Novick R. NSAID-analgesia, pain control and morbidity in cardiothoracic surgery. *Can J Anaesth* 2006; 53:46-59.
14. Griffin M. Con: Nonsteroidal anti-inflammatory drugs should not be routinely administered for postoperative analgesia after cardiac surgery. *J Cardiothorac Vasc Anesth* 2000; 14:735-738.
15. Ott E, Nussmeier NA, Duke PC, Feneck RO, Alston RP, Snabes MC, Hubbard RC, Hsu PH, Saidman LJ, Mangano DT. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 2003; 125:1481-1492.
16. Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoeft A, Parlow JL, Boyce SW, Verburg KM. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005; 352:1081-1091.
17. FDA U.S.Food and Drug Administration. Public Health Advisory - FDA announces important changes and additional warnings for COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm150314.htm, June 8, 2013.
18. Base de Données Publique des Médicaments / République Française. KETOPROFENE MEDAC 100 mg/4 mL, solution à diluer pour perfusion - Résumé des caractéristiques du produit. http://base-donnees-publiquemedicaments-gouvfr/affichageDocphp?specid=67834521&typedoc=R 2016
19. Reuben SS, Connelly NR, Lurie S, Klatt M, Gibson CS. Dose-response of ketorolac as an adjunct to patient-controlled analgesia morphine in patients after spinal fusion surgery. *Anesth Analg* 1998; 87:98-102.
20. Barden J, Derry S, McQuay HJ, Moore RA. Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults. *Cochrane Database Syst Rev* 2009; 4:CD007355.
21. Riou B, Plaisance P, Lecomte F, Soulat L, Orcel P, Mazoit JX. Comparison of two doses of ketoprofen to treat pain: A double-blind, randomized, noninferiority trial. *Fundam Clin Pharmacol* 2012; 28:20-28.
22. Harirforoosh S, Jamali F. Renal adverse effects of nonsteroidal anti-inflammatory drugs. *Expert Opin Drug Saf* 2009; 8:669-681.
23. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: A KDIGO summary (Part 1). *Crit Care* 2013; 17:204.
24. Stouten EM, Armbruster S, Houmes RJ, Prakash O, Erdmann W, Lachmann B. Comparison of ketorolac and morphine for postoperative pain after major surgery. *Acta Anaesthesiol Scand* 1992; 36:716-721.
25. Rapanos T, Murphy P, Szalai JP, Burlacoff L, Lam-McCulloch J, Kay J. Rectal indomethacin reduces postoperative pain and morphine use after cardiac surgery. *Can J Anaesth* 1999; 46:725-730.
26. Hynninen MS, Cheng DC, Hossain I, Carroll J, Aumbhagavan SS, Yue R, Karski JM. Non-steroidal anti-inflammatory drugs in treatment of postoperative pain after cardiac surgery. *Can J Anaesth* 2000; 47:1182-1187.
27. Maddali MM, Kurian E, Fahr J. Extubation time, hemodynamic stability, and postoperative pain control in patients undergoing coronary artery bypass surgery: An evaluation of fentanyl, remifentanil, and nonsteroidal antiinflammatory drugs with propofol for perioperative and postoperative management. *J Clin Anesth* 2006; 18:605-610.
28. Gust R, Pecher S, Gust A, Hoffmann V, Bohrer H, Martin E. Effect of patient-controlled analgesia on pulmonary complications after coronary artery bypass grafting. *Crit Care Med* 1999; 27:2218-2223.
29. Day RO, Graham GG. Non-steroidal anti-inflammatory drugs (NSAIDs). *BMJ* 2013; 346:f3195.
30. Angst MS, Clark JD, Carvalho B, Tingle M, Schmelz M, Yeomans DC. Cytokine profile in human skin in response to experimental inflammation, noxious stimulation, and administration of a COX-inhibitor: A microdialysis study. *Pain* 2008; 139:15-27.
31. Lavand'homme PM, Roelants F, Waterloos H, De Kock MF. Postoperative analgesic effects of continuous wound infiltration with diclofenac after elective cesarean delivery. *Anesthesiology* 2007; 106:1220-1225.
32. Carvalho B, Lemmens HJ, Ting V, Angst

MS. Postoperative subcutaneous instillation of low-dose ketorolac but not hydromorphone reduces wound exudate concentrations of interleukin-6 and interleukin-10 and improves analgesia following cesarean delivery. *J Pain* 2013; 14:48-56.

33. Lizarraga I, Chambers JP, Johnson CB. Prevention of N-methyl-D-aspartate-induced mechanical nociception by intrathecal administration of ketoprofen and ketamine in sheep. *Anesth Analg* 2008; 107:2061-2067.
34. Martin F, Fletcher D, Chauvin M, Bouhassira D. Constitutive cyclooxygenase-2 is involved in central nociceptive processes in humans. *Anesthesiology* 2007; 106:1013-1018.
35. Eisenach JC, Curry R, Tong C, Houle TT, Yaksh TL. Effects of intrathecal ketorolac on human experimental pain. *Anesthesiology* 2010; 112:1216-1224.
36. Eisenach JC, Curry R, Rauck R, Pan P, Yaksh TL. Role of spinal cyclooxygenase in human postoperative and chronic pain. *Anesthesiology* 2010; 112:1225-1233.
37. Spofford CM, Ashmawi H, Subieta A, Buevich F, Moses A, Baker M, Brennan TJ. Ketoprofen produces modality-specific inhibition of pain behaviors in rats after plantar incision. *Anesth Analg* 2009; 109:1992-1999.
38. Prado WA, Pontes RM. Presurgical ketoprofen, but not morphine, dipyrone, diclofenac or tenoxicam, preempts postincisional mechanical allodynia in rats. *Braz J Med Biol Res* 2002; 35:111-119.
39. Benhamou D, Bouaziz H, Zerrouk N, Preaux N. Audit of ketoprofen prescribing after orthopedic and general surgery. *Can J Anaesth* 1999; 46:109-113.
40. Sunshine A, Olson NZ. Analgesic efficacy of ketoprofen in postpartum, general surgery, and chronic cancer pain. *J Clin Pharmacol* 1988; 28:S47-S54.
41. Delage N, Maaliki H, Beloeil H, Benhamou D, Mazoit JX. Median effective dose (ED50) of nefopam and ketoprofen in postoperative patients: A study of interaction using sequential analysis and isobolographic analysis. *Anesthesiology* 2005; 102:1211-1216.
42. Oliveri L, Jerzewski K, Kulik A. Black box warning: Is ketorolac safe for use after cardiac surgery? *J Cardiothorac Vasc Anesth* 2014; 28:274-279.
43. Kulik A, Bykov K, Choudhry NK, Bateman BT. Non-steroidal anti-inflammatory drug administration after coronary artery bypass surgery: Utilization persists despite the boxed warning. *Pharmacoepidemiol Drug Saf* 2015; 24:647-653.
44. Kumar AB, Suneja M, Bayman EO, Weide GD, Tarasi M. Association between postoperative acute kidney injury and duration of cardiopulmonary bypass: A meta-analysis. *J Cardiothorac Vasc Anesth* 2012; 26:64-69.
45. Acharya M, Dunning J. Does the use of non-steroidal anti-inflammatory drugs after cardiac surgery increase the risk of renal failure? *Interact Cardiovasc Thorac Surg* 2010; 11:461-467.
46. Arora P, Kolli H, Nainani N, Nader N, Lohr J. Preventable risk factors for acute kidney injury in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 2012; 26:687-697.
47. Cawthorn TR, Phelan R, Davidson JS, Turner KE. Retrospective analysis of perioperative ketorolac and postoperative bleeding in reduction mammoplasty. *Can J Anaesth* 2012; 59:466-472.
48. Jian M, Li X, Wang A, Zhang L, Han R, Gelb AW. Flurbiprofen and hypertension but not hydroxyethyl starch are associated with post-craniotomy intracranial haematoma requiring surgery. *Br J Anaesth* 2014; 113:832-839.