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Comparing the impact of OFA (opioid free anesthesia) and steroids on the quality of recovery after Hip Arthroplasty by Direct Anterior Approach Using Minimally Invasive Surgery: a case-control study

C. Korthoudt (*), J. Van Lommel (**), M. Vandekerckhove (**), J. De Rycke (**), J. Mulier (***,****,*****)

Abstract: The direct anterior approach (DAA), a hip replacement method is less invasive showing superior early outcomes than in other approaches, both in terms of reduced pain and improved mobility. Our hypothesis is that patients undergoing total hip arthroplasty with direct anterior approach, who had OFA in combination with Methylprednisolone have a substantial lower CRP postoperative, a better quality of recovery and less use of opioids peri-operative than the control group. A case control study with 41 patients undergoing DAA were included. The study group got a classic OFA with high dose metylprednisolone 125 mg. A classic opioid anesthesia was used in the control group without the corticoid. A linear regression is used to evaluate the independent effect of the study group next to the effect of age/BMI/ASA/gender on morphine peri-operative used, QoR15 and CRP after 24h. Dindoo-Clavien score, PONV and length of hospital stay were evaluated secondary. Only BMI differed in the demographic characteristics between both groups, it was higher in the control group. OFA & steroids patients recovered better with lower CRP (11,5±3,0 vs 35±12,9 mg/dL; p=0,002) and higher QoR15 (127±7 vs 112±10; p=0,019) while getting a lower total dose of opioids peri-operative (5,2±2,1 vs 31,5±6,1 mg; p<0,001). In a linear regression analysis OFA & steroids was the only independent factor improving the quality of recovery and reducing the peri-operative opioids for the same VAS score. The CRP was independent lower in patients getting an OFA & steroid. OFA and high dose steroids improve quality of recovery with lower CRP.

Keywords: Anesthesia and analgesia; Enhanced Recovery After Surgery (ERAS); Total Hip Arthroplasty (THA).

Introduction

Enhanced recovery after total hip arthroplasty (THA) (1, 2), recommends avoiding epidurals, suggests maintaining normothermia, using tranexamine acid, multimodal opioid sparing anesthesia and early mobilisation. No recommendations yet to favour a direct anterior approach (DAA), to give high dose steroids or to use opioid free anesthesia (OFA). However, the general Enhanced recovery after Surgery (ERAS) guidelines recommend already to use the lowest dose of opioids possible perioperative, to use the least invasive surgical incision and to block inflammatory reactions.

The DAA has less dislocation, uses a smaller incision without muscle incision and is therefore less invasive (3). OFA requires zero opioids intra operative and allows to use paradoxical less opioids postoperative (4). High dose glucocorticoid are very good blockers of inflammatory reactions (5, 6). Dexmedetomidine (7), lidocaine (8) and magnesium (9), that are part of the opioid free protocol block the sympathetic reactions and to some degree also the inflammatory reactions.

The DAA approach has become standard already for all procedures while OFA and high dose glucocorticoids is used at each anesthesiologist discretion.

Our hypothesis: Patients undergoing total hip arthroplasty with direct anterior approach, who had OFA in combination with Methylprednisolone have a substantial lower CRP postoperative, a better

C. Korthoudt, J. Van Lommel, M. Vandekerckhove, J. De Rycke, J. Mulier
(*) Department of Anaesthesiology and reanimation, Antwerp University Hospital, 2650 Edegem, Belgium.
(**) Department of Orthopedics, AZ Sint Jan Brugge-Oostende, Campus Brugge, 8000 Brugge,Belgium.
(***) Department of Anesthesiology, Intensive Care and Reanimation, AZ Sint Jan Brugge-Oostende, Campus Brugge, 8000 Brugge, Belgium.
(****) KU Leuven, University of Leuven, 3000 Leuven, Belgium.
(*****) UGent, University of Gent, 9000 Gent, Belgium.
Corresponding author: Korthoudt C., Drie Eikenstraat 655, 2650 Edegem.
Email : christophe.korthoudt@hotmail.com

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quality of recovery and less use of opioids perioperative than the control group, opioid anesthesia without corticoids.

Methods

The OFA in combination with a high dose methylprednisolone was used in a limited group of patients in the period of November 2018 to September 2019. A control group of patients with opioid anesthesia without corticoids in the same period was constructed based on inclusion criteria. Local ethical committee approval was granted for a retrospective observational study and STROBE-statement checklist was followed.

Patients were included if the procedure was performed under general anesthesia with measurement of NMT, BIS and ANI, if pre and post operative CRP values were available, if a QoR15 questionnaire was filled out, an Apfel score could be made and sufficient post operative data on opioid consumption and VAS score was available.

The minimally invasive direct anterior approach (DAA) and a 'bikini' incision requires a general anesthesia with the patient in the supine position. The internervous and intramuscular Heuter interval was used to approach to the hip joint. A cementless femoral component (Taperloc Complete System, Zimmer Biomet, Warsaw) combined with a cementless acetabular component (G7 Acetabular System / Allofit IT Acetabular System, Zimmer Biomet, Warsaw) was used for all cases.

Immediate full weight bearing was allowed and a standard rehabilitation program was started on the first day after surgery.

OFA was defined as the administration of no opioids either pre- or intraoperatively until wound closure. Postoperative opioids after OFA were only given when the patient was fully awake and had been administered nonopioid analgesics previously.

Data collection and statistics

The following demographic data were retrieved out of the medical file: age; Body Mass Index (BMI); American Society of Anesthesiologists (ASA) physical status class; history of hypertension, current or recent smoking, motion sickness, or previous postoperative Nausea and vomiting (PONV).

The presence of perioperative complications during the first postoperative month was graded according to the modified Clavien-Dindo (CD) classification (11). The CD grades were converted to six categories for use in the statistical analysis, with grades 1, 2, 3a, 3b, 4a, and 4b converted to category 1, 2, 3, 4, 5, and 6, respectively (12). Length of hospital stay (LOS) was calculated as the number of nights spent in the hospital postoperatively.

The simplified Apfel score (based on non-smoking status, female sex, history of previous PONV or motion sickness, and postoperative opioid use) was calculated for each patient (13), and the presence of nausea or vomiting, was retrieved out of the medical file. We likewise retrieved the maximum visual analog scale (VAS) and opioid usage during the first 24 hours postoperatively. Opioid usage for same VAS score's was converted to total iv morphine equivalents as follows: 1 mg iv morphine =1 mg iv or subcutaneous piritramide, 10 mg iv tramadol, or 2 mg sublingual oxycodone (14).

C-reactive protein (CRP), LOS and QoR-15 pre- and postoperative was also retrieved out of the medical file. The QoR-15 is a developed patient-reported outcome measurement of postoperative quality of recovery, calculated out of 15 questions (1= never; 5= all of the time). It was developed from the larger QoR-40, which has been extensively used and validated as a measurement of postoperative quality of recovery. The QoR-15 had equivalent psychometric properties compared with the QoR-40, but was more feasible to use (15).

The demographic data and clinical outcome parameters are expressed as the means and standard deviations and were either analyzed using the Kolmogorov-Smirnov test or expressed as a percentage of cases and analyzed using the χ^2 test. A linear regression analysis was used to determine the independent effects of different factors on the outcome parameters. Scoring will be compared between both groups using a Kolmogorov-Smirnov test with $p < 0,05$. Statistical analyses were performed using the statistical package Stata/IC 15.1 for Mac (StataCorp, TX, USA).

Results

There were 21 patients found with an OFA and high dose glucocorticoid that qualified for the study. 20 patients in the OA group were found and qualified for inclusion. The demographic and clinical characteristics of OFA & steroids versus OA groups are shown in Table 1. The BMI was higher in the OA group. There was no difference regarding age, gender, ASA score, CRP and QoR15 preoperative, smoking, history of previous PONV or motion sickness, and Apfel score combining gender, PONV history, smoking and opioid use postoperative.

Table 1

Demographic data

	OFA (n=21)	OA (n=20)	p value	test
Age (years)	69.16 +/- 5.105	68.272 +/- 5.28	0.989	Kolmogorov-Smirnov
gender (male)	38.8 %	59.1%	0.155	z-score
BMI	25.935 +/- 1.852	29.848 +/- 2.146	0.031	Kolmogorov-Smirnov
ASA score	1.846 +/- 0.484	1.923 +/- 0.521	1.0	Kolmogorov-Smirnov
Hypertension	47.1 %	47.6 %	0.973	z-score
Smoker	22.2 %	22.7 %	0.970	z-score
CRP pre op	2.543 +/- 2.41	4.782 +/- 5.781	0.146	Kolmogorov-Smirnov
QoR15 pre op	130.222+/- 7.457	132.667+/- 6.475	0.964	Kolmogorov-Smirnov
apfel score	2.611+/- 0.487	2.095+/- 0.453	0.725	Kolmogorov-Smirnov

OFA: opioid free anesthesia, OA: opiod anesthesia, BMI: body mass index, CRP: C-reactive protein, QoR15: quality of recovery score on 15 questions.

Both groups got Propofol 2 to 3 mg kg^{-1} at induction followed by sevoflurane 1,8 to 2,3% end tidal inhalation to achieve accurate depth of anesthesia verified by BIS. Neuromuscular blockade was achieved by the administration of 0,6 to 1 mg kg^{-1} rocuronium followed by a continuous infusion aimed at achieving a deep neuromuscular block measured by post-tetanic count (PTC<5) as requested by the surgeons.

All patients received an antibiotic prophylaxis with cefazoline 2gr. To prevent bleeding, patients got tranexamic acid 1gram intra-venous (iv) loading dose before incision and 1gram iv bolus dose before extubation.

The method by which OFA was administered in the study group consisted mainly of combining Dexmedetomidine, Lidocaine, Ketamine and Magnesium. Dexmedetomidine was administered as follows: 0.25 mcg kg^{-1} 15 minutes before induction, 0.1 mcg kg^{-1} at induction, and an infusion of 0.1 mcg kg^{-1} h^{-1} for maintenance. Lidocaine was administered as 1 mg kg^{-1} at induction, followed by an infusion of 1 mg kg^{-1} h^{-1} for maintenance. Ketamine was administered as 0.1 mg kg^{-1} at induction, 0.7 mg kg^{-1} (maximum, 50 mg) before incision, and an infusion of 0.1 mg kg^{-1} h^{-1} for maintenance. Magnesium was loaded at induction as a bolus of 40 mg kg^{-1} without further continuation. Extra 10 to 20 mcg dexmedetomidine was given based on hemodynamic reactions and on monitoring the analgesia nociception index (ANI) to achieve values above 40 (10). Postoperative analgesia was continued with low doses of dexmedetomidine (0.05 mcg kg^{-1} h^{-1}), ketamine (0.05 mg kg^{-1} h^{-1}), and lidocaine (0.5 mg kg^{-1} h^{-1}) for the first few hours (maximum, 5 hours) after surgery, with a maximal bolus dose of 10 mg lidocaine, 1 mg ketamine, and 1 mcg dexmedetomidine administered every 15 minutes on an as-needed basis. All patients in study group got also a high dose Methylprednisolone (125 mg Solumedrol) before incision, repeated post-operative at 24 h on the ward.

Sufentanil were administered in the control group at a dose of 0.1-0.3 mcg kg^{-1} at induction, followed by additional 0.1-0.2-mcg kg^{-1} doses during surgery based on hemodynamic reactions and to achieve ANI values above 40. The control group got no steroids, dexmedetomidine, clonidine, lidocaine, ketamine or magnesium.

Every patient got a pericapsular injection that includes a mixture of 100mL ropivacaine 0,2% and 0,3 mg adrenaline to prolong its effect.

All patients received before awakening a rapid loading dose of 1 gram Paracetamol iv over 5 minutes (TBW < 75 kg) or 2 gram (TBW > 75 kg and no renal impairment) at end of surgery and Ketorolac 0,5 mg kg^{-1} IBW.

The clinical outcome of both groups is given in table 2. There was no difference in the number of patients having nausea or vomiting, in the number of therapeutic anti emetics given, in the maximum VAS score, dose of opioids given postoperative and LOS. The OFA & steroids group got less prophylactic antiemetic drugs. OFA & steroids patients recovered better with lower CRP and higher QoR15 score while getting a lower total dose of opioids perioperative.

Table 2

Outcome parameters

	OFA (n=21)	**OA (n=20)**	**p value**	**test**
Nausea (%)	5.6 %	27.8 %	0.099	z-score
Number of therapeutic anti emetic drugs	0.125+/-0.182	0.500+/-0.352	0.063	t-test
Max VAS score (%)	4.842+/-1.298	5.00+/-1.35	0.861	t-test
total dose of morphine perioperative	5.237+/-2.094	31.548 +/- 6.087	< 0.001	Kolmogorov-Smirnov
QoR15 24H post op	126.533 +/-7.289	111.579+/-9.831	0.019	Kolmogorov-Smirnov
CRP 24H postop	11.528+/-2.998	35.073+/-12.894	0.002	Kolmogorov-Smirnov
No need of any opioid postoperative %	22.2%	23.8%	0.686	z-score
CD grading	0.1	0.409	0.019	pearson corr
LOS	2.33+/-0.24	3.05+/-0.63	0.051	Kolmogorov-Smirnov

OFA: opioid free anesthesia, OA: opiod anesthesia, VAS: visual analog score, QoR15: quality of recovery score on 15 questions, CRP: C reactive protein, CD: Clavien-Dindoo, LOS: length of hospital stay).

Table 3

Regression analysis of QoR15, Perioperative opioids, max VAS score and LOS

	QoR15 24h postoperative		**opioids perioperative**		**highest VAS score postoperative**		**LOS**	
	coef	p	coef	p	coef	p	coef	p
age	0.255	0.452	-0.537	0.002	-0.097	0.064	-0.009	0.471
gender	8.549	0.327	-3.437	0.379	-1.546	0.220	0.64	0.068
BMI	0.789	0.410	0.613	0.152	0.002	0.238	-0.154	0.002
OFA	19.349	0.040	-23.615	<0.001	-0.865	0.487	-1.635	<0.001
QoR15preop	0.384	0.190	0.165	0.200	-0.043	0.291	-0.064	<0.001

QoR15: quality of recovery score on 15 questions VAS: visual analog score ; LOS: length oof hospital stay; BMI: body mass index, OFA opioid free anesthesia.

Table 4

Regression analysis of CRP

	CRP	
	coef	p
age	0.792	0.052
gender	2.356	0.796
BMI	-0.371	0.750
OFA	**-28.412**	**0.015**

CRP: C-reactive protein, BMI: body mass index.

Table 5

Regression analysis of PONV

	PONV	
	coef	p
age	0.069	0.238
apfel score	**1.368**	**0.035**
BMI	-0.056	0.652
OFA based on no intra op opioids	**-3.088**	**0.039**

BMI: Body mass index, PONV: postoperative nausea and vomiting, OFA: opioid free anesthesia.

There were no major complications in both groups but total complications graded by Clavien-Dindoo was lower in the OFA group (2 vs 9).

In a linear regression analysis OFA & steroids was the only independent factor improving the quality of recovery as shown in table 3 when age, gender, BMI, preoperative QoR15, history of PONV were taken into account as cofactors.

In a linear regression analysis with the same cofactors OFA & steroids and older age reduced the total perioperative dose of morphine equivalent given. Max VAS score was not related to OFA or

any of the cofactors. LOS was shorter in the OFA & steroids group and also in patients with a higher BMI and a higher QoR score pre-operative.

The CRP was lower in patients getting OFA and steroids, see table 4.

Table 5 shows PONV is lower in patients with a lower Apfel score and in patients getting OFA & steroids.

Discussion and conclusion

The study has some limitations. For a retrospective study the groups were very small, what intends less power of the outcome parameters. Nevertheless we found a significant lower CRP and higher QoR15 in our study group.

Both groups, although matched for several factors were not equal with a 4 points higher BMI in the control group what might have a clinical impact. Therefore we used BMI as one of the co factors in every regression analysis.

This small study group revealed no significant difference in history of previous PONV or motion sickness, however 28% of patients in OFA group had a history of PONV versus 9% in the OA group what would have required a larger study group to improve an equal spread and avoid any impact. PONV probably was therefore not significant higher (28%) in the control group versus OFA (6%) but when a regression analysis was done with Apfel score, BMI and age as cofactors, a low Apfel score and OFA reduced independent the incidence of PONV conforming the superiority of OFA versus OA and prophylactic drugs.

Ziemann-Gimmel et al.(16) found indeed that triple prophylaxis is less effective compared to OFA and previous studies revealed less PONV in OFA (17). As no major complication with a CD > II took place PONV was one of the most frequent side effects.

The outcome shows a difference in quality of recovery, CRP and CD grading and not for LOS. VAS score was also equal indicating a good pain management. Total dose of Morphine peri-operative was lower in the OFA group but the postoperative dose and the number of patients requiring opioids postoperative was not different probably again due to the small study group.

Quality of recovery combines pain, PONV and other less frequent problems and was higher after OFA.

The regression analysis repeats the association of only OFA with the quality of recovery or QoR-15 24 h postoperative. The total dose of perioperative opioids is lower in OFA and older patients and VAS score was equally treated in both groups even when co factors were taken into account making the opioid dose consumed more reliable.

Deep neuromuscular block till closure of fascia was not achieved in every patient. The ANI above 40 was achieved in every case. CRP as a measure of total inflammatory reaction on surgical stress was measured after 24 hours and found to be lower in OFA & steroid group even with both groups achieving no sympathetic stress by ANI measurements.

Another limitation is that we cannot distinguish between the steroid effect and the OFA effect and we cannot verify an additive effect. We knew already from previous studies that high dose steroids combined with opioids improved outcome and reduced postoperative analgesia requirements in THA. In comparison of our study with Lunn et al. (6) where CRP postoperative in our study group almost equal to pre-operative. OFA alone reduces also CRP compared to opioid anesthesia in laparoscopic surgery (17) but no information is available yet in THA.

To conclude, OFA & high dose steroids improves quality of recovery with lower CRP and less need of peri-operative opioids. This case control study indicates that further investigation is necessary and could be useful in clinical practice.

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