Title:
A randomised, double-blind, placebo-controlled trial on the efficacy of dexamethasone combined with neuraxial anaesthesia in reducing pain and opioid consumption after primary cementless total hip arthroplasty using the direct anterior approach.

Background:
There is increasing evidence that intra-operative intravenous high-dose glucocorticoids decreases postoperative pain and opioid use after total hip and knee replacement. Randomised studies comparing the effect of intra-operative dexamethasone with placebo in patients receiving neuraxial anaesthesia (NA) are lacking.

Methods:
Ninety consecutive patients undergoing THA via DAA with NA were randomised to two groups to either receive a single dose of 10-mg dexamethasone IV or a placebo (isotonic saline IV) intra-operative. Both groups received the same standard peri-operative anaesthesia protocol. All patients were operated by a single surgeon. Primary outcomes were pain level measured through visual analogue score (VAS) at 1-,3-,6-, 12- and 24-hours post-operative; opioid use measured as a sum of morphine milligram equivalents (MME); and range of motion (ROM) 24 hours post-operative. Secondary outcomes were time-up-and-go (TUG) test and in hospital complications.

Results:
There were no differences in age, gender, body mass index (BMI), or American Society of Anaesthesiologists (ASA) score between the groups. Patients receiving intra-operative dexamethasone reported statistically significantly lower MME compared to placebo (6.4 ± 12.8 vs. 16.9 ± 24.7, p=0.01). VAS score 1-hour postoperatively was higher in the dexa group (0.8 ± 1.5 vs 0.2 ± 0.7, p=0.02). All other VAS scores were lower in the dexamethasone group, however only 6- and 12 hours postoperative reached significance (respectively $2,2 \pm 1.8$ vs 3.0 ± 2.2 and 2.7 ± 2.0 vs 3.7 ± 2.4; p=0.05 and p=0.03). There were no differences in post-operative ROM and TUG test between groups. C-reactive-protein levels day 1 postoperative were significantly lower in the dexa group (18.5 ± 13.9 vs 28.6 ± 21.4, p=0.009). There were no complications due to the administration of dexamethasone.

Conclusion:
The administration of intra-operative dexamethasone effectively reduces opioid use and pain levels post-operative in patients undergoing THA with NA without any adverse effects. Incorporation of intra-operative dexamethasone in anaesthesia protocols together with neuraxial anaesthesia leads to superior clinical outcomes that could benefit the transition from inpatient to outpatient THA.

Keywords:
Direct Anterior Approach, Dexamethasone, Neuraxial Anaesthesia, Total Hip Arthroplasty, Glucocorticoids

Background

As the need for total hip replacements is projected to increase by 71% by 2030 (1), surgeons are increasingly compelled to reduce costs and hospitalization time. Today, outpatient THA is gaining popularity and it is expected that by 2050 50% of all THA will be performed in outpatient setting (2). In the year 2020 alone, driven by the COVID-19 pandemic, outpatient THA and TKA increased by 82% in the North-eastern region of the United States (3).

Enhanced recovery after surgery (ERAS) protocols have been the driving force behind shorter hospitalization times (4)(5), combined with soft tissue sparing techniques and innovations in surgery and anaesthesia (6). However, despite the protocols abounding, some limitations such as postoperative nausea and vomiting (PONV), pain and distress and opioid use are still encountered (5).

In recent years, glucocorticoids have gained popularity in ERAS protocols to counter these postoperative complications (5)(8). Glucocorticoids exert their analgesic effect through inhibiting pain receptors at the spinal level and by reducing the production of inflammatory prostaglandins and leukotrienes by inhibiting arachidonic acid production (9). Expected complications of glucocorticoids such as alterations in perioperative glycemia, infection and impaired wound healing do not occur when giving a single high dose of glucocorticoids (10)(11)(12)(13).

Multiple studies have already demonstrated a reduced LOS, PONV, pain and opioid use in patients who received THA under general anaesthesia (14)(15)(16). However, to date, this has never been investigated in randomized studies for patients who received THA via DAA under neuraxial anaesthesia.

Materials & Methods

The trial was approved by the institutional Ethics Committee of AZ Sint-Lucas Bruges. All patients gave oral and written informed consent before participation into the study. Ninety consecutive patients who met the inclusion criteria were enrolled in this prospective, double-blind, randomised trial. All adult patients receiving elective, unilateral, primary THA were included. Exclusion criteria included revision THA, fractures, avascular necrosis, intolerance to corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDS), pre-operative corticosteroid use (<3 months), patients not fit for NA and the presence of rheumatoid disease, systemic lupus erythematosus, and ankylosing spondylitis.
Patients were randomly assigned to 2 groups using a computer-generated randomization tool (www.randomizer.org). The experimental group (dexa group) received 1 dose of 10mg intravenous dexamethasone intra-operative. The control group received 1 dose of isotone sodium-saline solution intra-operative. Only the anaesthesiologists were aware of the intervention, but they were not involved in any way in the data processing and analysis. The surgeon, the patient, nurses, and the data controller and analyst were blinded to the intervention. Post-operative anaesthesia protocols were identical for both groups. Opioids were only given if standard analgesics were inadequate. All surgery was performed by a single senior surgeon with broad experience in THA via direct anterior approach (DAA). All

patients received NA. NA dosing consisted of 6-8mg of bupivacaine administered intraspinal. Low-molecular weight heparin was started the day of surgery and continued for 4 weeks. Primary outcomes were pain level measured through visual analogue score (VAS) pre-operative and at 1-,3-,6-, 12- and 24-hours post-operative; opioid use measured as a sum of morphine equivalents (MME); and range of motion (ROM) 24 hours post-operative. Secondary outcomes were time-up-and-go (TUG) test, and in hospital complications.

Statistical analysis

Based on results of former studies (12)(17), the average difference in VAS score was 0,70 between groups. With a power of 0.90 and significance level of 0.05, the sample size required calculation was 40 for each arm. We included 45 patients in each group.,
All statistical analyses were performed using SPSS statistics 27.0 (SPSS Inc., Chicago, IL, USA). The independent student's test was used to compare mean differences between groups. Fisher's exact test was used to compare mean differences of categorical variables. Statistical significance was set at $p < 0.05$.

Results

Patient demographics were similar in both groups (Table 1). VAS scores preoperatively did not differ between both groups (6.2 vs 6.7, $p > 0.5$) (Table 2). Overall pain was significantly reduced after surgery during hospitalisation. VAS scores were significantly lower in the dexa group at 6- and 12-hours postoperative compared to controls (respectively 2.2 vs 3.0 and 2.7 vs 3.7; $p = 0.05$ and $p= 0.03$). VAS score 1-hour postoperatively was higher in the control group vs the dexa group (0.8 vs 0.2, $p = 0.02$), VAS scores at 3- and 24-hours postoperative were not significantly different (1.5 vs 1.1, $p > 0.5$ and 2.4 vs 2.6, $p > 0.5$). There was a considerable decrease in MME in the dexa group compared to the control group (6.4 vs. 16.9, $p = 0.01$). Haemoglobin levels postoperative were similar in both groups (12.1 vs 11.9, $p = 0.44$), also there was no difference in haemoglobin decline postoperatively (2.1 vs 2.5, $p > 0.05$) (Table 3). CRP levels were higher in the control group (18.5 vs 28.6, $p = 0.01$) and CRP rise postoperative was higher in the control group (15.2 vs 24.2, $p = 0.04$). There was no difference in TUG test between groups (25.9 vs 31.7, $p = 0.06$), nor was there any difference in ROM. There were no in hospital complications, nor any infections in either group during follow-up.

Discussion

This randomised, double blind, placebo-controlled trial compared the effect of administering a single dose of 10-mg dexamethasone intraoperative in patients undergoing elective THA via DAA under NA.
The main findings in this study were the significant decrease by a factor of 2.6 in opioid use and lower VAS scores at various time intervals postoperatively. However, there were no significant differences in ROM and TUG test, nor in complications of any kind.

These findings are consistent with a previous study conducted by Kelly et al.(18), who retrospectively reviewed 164 patients that received intra-operative dexamethasone during THA via DAA under NA and compared these to 212 control cases. Patients who received dexamethasone had a significant decreased opioid use postoperative (8.57 vs 11.44, $p = 0.001$) and postoperative NRS pain score was lower in the dexa group (1.6 vs 2.3, $p = 0.014$).

Stratification by dose of received dexamethasone showed no significant differences. Although the minimal clinically important difference (MCID) of the VAS pain score of 1.5 for THA was not reached at any moment postoperative, the MCID of 10 MME for opioid use however was clearly exceeded (19). Whether this is due to the higher dose of dexamethasone or coincidental is unclear. A meta-analysis of RCTs by Lex et al (20) showed that higher or repeated doses have an additional benefit in reducing pain. A more recent meta-analysis, however, could not find strong evidence to determine the optimal dose or the optimal number of doses (21).

PONV and opioid use have been suggested as to be the main reason for prolonged length of stay (LOS) after THA (22). With the ever-increasing need for THA and a growing financial burden on the health care system (23), we believe it is of critical importance to reduce LOS and promote outpatient THA. Studies have already shown that outpatient THA significantly reduces costs from a consumer perspective, as well as from a societal perspective (24)(25)(26). Countering these postoperative complications is therefore of clinical and economical importance.

The TUG test was found to be lower by 6 seconds in the dexa group. Although this difference was not significant, significance was almost met ($p = 0.06$). We believe that the effect of dexamethasone on mobility is indirect, in the sense that postoperatively it reduces pain and opioid-induced imbalance and, as a result, patients start to mobilise faster. ROM did not differ between the groups, which was to be expected as it mainly depends on component placement (26).

NA has already proved to be superior to GA regarding minor postoperative complications such as PONV, narcotic use and same day discharge appears to be more successful in patients receiving NA vs GA (33% vs 23.4%, $p < 0.01$) (27). A small increase in major complications such as pneumonia, systemic infections, critical care utilization, and inpatient falls is seen in patients receiving GA (28). We therefore believe combining NA and perioperative administration of dexamethasone could lead to improved outcomes of THA and could further improve the ongoing transition from inpatient to outpatient THA.

There are some limitations to be noted in this study: 1) This is a single centre and single surgeon study and therefore some caution is needed in extrapolating these results; 2) Although patients were followed up to 1 year postoperatively and no complications were seen, follow-up in this study for primary outcomes was limited to 24 hours; 3) There was no comparison of dosage in this study.

Conclusion

The administration of intra-operative dexamethasone effectively reduces opioid use and pain levels post-operative in patients undergoing THA with NA without any adverse effects. Incorporation of intra-operative dexamethasone in anaesthesia protocols together with neuraxial anaesthesia leads to superior clinical outcomes that could benefit the transition from inpatient to outpatient THA.

Table 1 Patient demographics

	Dexa group	Control group	p value
N	45	45	/
ASA	1.7 ± 0.5	1.8 ± 0.4	0.51
Sex			0.46
Male	27	28	
Female	18	17	
Age	66.4 ± 9.69	67.4 ± 9.1	0.88
BMI	26.6 ± 4.08	27.2 ± 4.1	0.48

N: Sample size; ASA: American Society of Anaesthesiologists; BMI: Body Mass Index

Table 2 Outcome measures

	Dexa group	Control Group	p Value
VAS preoperative	6.2 ± 2.5	6.7 ±1.8	0.26
VAS 1h	0.8 ± 1.5	0.2 ± 0.7	**0.02**
VAS 3h	1.5 ± 1.8	1.1 ± 1.6	0.37
VAS 6h	2.2 ± 1.8	3.0 ± 2.2	**0.05**
VAS 12h	2.7 ± 2.0	3.7 +-2.4	**0.03**
VAS 24h	2.4 ± 2.0	2.6 ± 2.0	0.67
MME	6.4 ± 12.8	16.9 ± 24.7	**0.01**
TUG	25.9 ± 12.8	31.7 ± 14.7	0.06
ROM° (flexion)	86.9 ± 21.5	87.6 ± 18.7	0.89
ROM° (extension)	7.7 ± 12.2	8.8 ± 11.9	0.67
ROM° (exorotation)	25.1 ± 10.6	26.4 ± 11.8	0.75
ROM° (endorotation)	20.5 ± 10.4	19.6 ± 14.2	0.61

VAS: Visual analogue score; MME: morphine milligram equivalents; TUG: Time-up-and-go-test; ROM: Range of motion

Table 3 Blood values

	Dexa group	Control group	p value
Hb_{pre}	14.2 ± 1.3	14.2 ± 1.3	0.9
CRP_{pre}	2.4 ± 3.7	5.3 ± 9.3	0.09
Hb_{post}	12.1 ± 1.6	11.8 ± 2.1	0.40
CRP_{post}	18.5 ± 13.9	28.6 ± 21.9	**0.01**
Hb_{pre}- Hb_{post}	2.1 ± 0.4	2.5 ± 1.5	0.37
CRP_{post}-CRP_{pre}	15.2 ± 13.0	24.2 ± 22.2	**0.04**

Hb: Haemoglobin; CRP: C-reactive-protein; pre: preoperative; post: postoperative

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