pharmacotherapy. Clearly the feasibility of these new approaches needs to be determined.

The recent correspondence of Hartley and colleagues[3] in the *British Journal of Anaesthesia* may help commence a discussion on whether we need to keep the current paradigm {drug dose–drug concentration–drug effect (both desired [efficacy] and undesired [side-effects])} or shift to a drug effect–drug concentration–drug dose paradigm!

They electronically captured vital signs of 15 newborn infants who were treated with morphine 0.1 mg kg^{-1} orally ~1 h before their clinical procedure for 24 h before and after the procedure to show that there was a wide variation in the baseline physiological stability of these infants.

Moreover, their analysis indicated that their approach was able to predict which infants are at risk of adverse events from the use of pain-relieving medicines, and also underscored the value of physiological monitoring to optimise use of pain-relieving medicines in individual neonates.

The authors state that their modelling approach might facilitate personalised drug dosing and ultimately safeguard infants against preventable iatrogenic harm.

This study has clearly shown that it is possible to use vital sign monitor data for the objective and continuous evaluation of physiological parameters in preterm infants. This is in stark contrast with the current practice of subjective, intermittent interpretations of physiological and clinical parameters. As such, this study shows that there is an incentive for bedside trend visualisation and more continuous and objective pharmacotherapeutic evaluation in unstable patients.

However, are we currently ready to forfeit PK information of drugs used in these settings for pain relief? In other words, are we ready to administer an amount of oral morphine to neonates based on only one study of oral morphine bioavailability in newborn infants, using the newly proposed method of objective and continuous evaluation of physiological parameters for personalised pain treatment.[3] Based on this evaluation the dose of morphine could be adjusted without any knowledge of the drug concentration in the individual patient to find the optimal amount for that unique patient. Or do we want to assure that the effect–concentration–dose relationship is still based on proper knowledge of PK in the vulnerable neonate. If the latter is the preferred path then we still need to measure drug concentrations in these tiny neonates, but based on the currently available knowledge on morphine PK in neonates[4] and the lack of a morphine concentration–response curve,[5] that might not be necessary anymore.

In summary, we must treat neonates suffering from pain with a clear PD endpoint: pain relief. The question is whether we can reach a clear and desired PD endpoint without having any PK information on the administered drug. Are we ready for that or is it still a bridge too far?

I think that we are ready for a paradigm shift from dose–concentration–effect towards effect–(concentration)–dose, especially in the growing number of NICUs that are capable of performing continuous evaluation of physiological parameters. The correspondence of Hartley and colleagues[3] supports the above-mentioned paradigm shift, but it might be premature for NICUs that are not able to objectively and continuously evaluate the physiological parameters of their patients.

Declarations of interest

The author declares that they have no conflict of interest.

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doi: 10.1016/j.bja.2021.01.012
Advance Access Publication Date: 12 February 2021

Opioid-free anaesthesia for anterior total hip replacement under general anaesthesia: the Observational Prospective Study of Opiate-free Anesthesia for Anterior Total Hip Replacement trial

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Keywords: dexmedetomidine; hip replacement; opioid-free anaesthesia; perioperative outcomes; postoperative analgesia

Editor—Intraoperative nociception is the consequence of the interactions of multiple noxious stimuli that promote peripheral and central sensitisation. Opioid-based anaesthesia increases postoperative complications and alters the immunomodulatory signalling pathways.[1] Dexmedetomidine (Dex), a selective α2-adrenergic receptor agonist, has sedative and analgesic properties, improves glial functions, and reduces postoperative oxidative stress and neuronal apoptosis.[2] To our knowledge, there is no information about the use of opioid-free anaesthesia (OFA) with Dex during total hip arthroplasty (THA) under general anaesthesia (GA).

After ethical approval (Comité de Protection des Personnes Est 1; No. SI 19.02.05.66548, ID RCB 2018-A03393-52; September 4, 2019), registration (NCT04112277; registered on September 30, 2019), and written informed consent, 100 patients aged 18–85 yr scheduled for primary unilateral THA using an anterior approach under GA were included from October 2019 to January 2020. The control group was retrieved from the electronic medical record and the anaesthesia information management system (DIANE; Bow Medical, Amiens, France) after consecutive analysis of all patients operated on during the 6 months preceding the start of the Observational Prospective Study of Opiate-free Anesthesia for Anterior Total Hip Replacement (ASOPHA) trial and meeting the criteria for inclusion, exclusion, and perioperative rehabilitation identical to those used in the ASOPHA trial, inclusion being discontinued after 100 patients were identified. This processing was authorised by the Ethics Committee and the Commission Nationale de l'Informatique et des Libertés (No. 2210577v0; December 19, 2018). With the exception of the use of sufentanil, the same perioperative multimodal analgesia and rehabilitation programme for THA was used in the two groups.

Premedication included paracetamol 1 g, ketoprofen 100 mg, and pregabalin 150 mg, all p. o. Patients received tranexamic acid 15 mg kg^{-1}, nefopam 20 mg, ketamine 0.5 mg kg^{-1}, droperidol 1.25 mg, dexamethasone 8 mg (all i.v.), and a peri-articular infiltration (levobupivacaine 0.5%). In the PACU, morphine i.v. was titrated (3 and 2 mg [5 min]$^{-1}$ in patients <60 kg) until pain numeric rating scale (NRS) score was ≤3. Patients were provided oral paracetamol 1 g (6 h)$^{-1}$, oral ketoprofen 100 mg (12 h)$^{-1}$, and oral immediate-release oxycodone 5 mg (4 h)$^{-1}$ (≤50 kg) or 10 mg (>50 kg) in case of NRS score >3. Postoperative nausea and vomiting (PONV) were treated by ondansetron 4 mg. Oxygen was administered for Spo_2 ≤94%. Patients were mobilised from the fourth postoperative hour. Home-discharge criteria were NRS score <3 at rest, ability to dress, ability to climb at least one stair, normal voiding, and absence of PONV and surgical complications. These criteria, determined for more than 4 yr in the orthopaedic rehabilitation process, were the same in the two groups.

General anaesthesia was induced with propofol 2 mg kg^{-1} and cisatracurium 0.2 mg kg^{-1}, and maintained with sevoflurane (air:O_2 50:50). In the OFA group, Dex (diluted to 4 μg ml^{-1} in sodium 0.9%) 0.7 μg kg^{-1} was infused over 20 min before induction using a standard syringe pump (Alaris® TIVA; CareFusion, Voisins le Bretonneux, France), continued at 1.5 μg kg^{-1} h^{-1} until the incision, gradually reduced by 0.5 μg kg^{-1} h^{-1} every 10–15 min, and interrupted at the time of acetabular component impaction, usually about 30 min before skin closure. In the control group, sufentanil was administered during the induction at the discretion of the anaesthetist, and afterwards based on cardiovascular responsiveness. Systolic arterial pressure (SAP) was maintained within 30% of baseline values by adjusting the sevoflurane concentration and, if necessary, boluses of urapidil 25 mg, ephedrine 6 mg, phenylephrine 50–100 μg, or atropine 0.5 mg i.v. Dexmedetomidine was interrupted when SAP ≤60 mm Hg or an HR <40 beats min^{-1} for 3 min. The primary outcome was the 24 h morphine equivalent consumption (excluding sufentanil). Secondary endpoints included NRS scores, vasoactive drugs, time between surgical closure to tracheal extubation, PONV, episodes of Spo_2 ≤94%, and hospital length of stay (LOS). Ninety-one patients per group were required to detect a 30% reduction in the primary outcome (α 0.05, power; β 0.9; reference: 24 h opioid requirement 16 [10] mg from the first 50 patients receiving sufentanil). Data were compared with two-tailed parametric or non-parametric tests as required. A multivariate analysis was performed to identify risk factors associated with 24 h opioid use.

Patient characteristics were comparable between groups (Supplementary Table 1). The mean dose of sufentanil administered intraoperatively in the control group was 0.41 (0.18) μg kg^{-1}. Opioid-free anaesthesia reduced the morphine equivalent consumption (0 [0–10] mg *vs* 10 [0–28] mg; P=0.002), the risk ratio (RR) of 24 h opioid requirement (RR: 0.69; 95% confidence interval [CI]: 0.52–0.91; P=0.009), and morphine titration (Table 1). In multivariate analysis (Supplementary Table 2), OFA was associated with lower odds of 24 h opioid consumption (odds ratio [OR]: 0.38; 95% CI: 0.16–0.90; P=0.028), whilst NRS score ≥4 in PACU was associated with higher risk (OR: 2.48; 95% CI: 1.97–3.12; P<0.001). Numeric rating scale scores were significantly improved by OFA (Supplementary Fig 1). Opioid-free anaesthesia increased ephedrine consumption (mean difference: 3.0 mg; 95% CI: 0.3–5.8 mg; P=0.035) without differences in vasopressor or atropine use. Opioid-free anaesthesia prolonged the extubation time (mean difference: 7.0 min; 95% CI: 3.6–10.5 min; P<0.001) without impact on PACU discharge (Table 1). Opioid-free anaesthesia reduced O_2 requirement in PACU (RR: 0.68; 95% CI: 0.53–0.88; P=0.003) and at 24 h (RR: 0.41; 95% CI: 0.18–0.95; P=0.04). Patients were discharged earlier in the OFA group (mean difference: −1.3 days; 95% CI: −2.1 to −0.6 days; P<0.001).

Our data provide relevant information of an OFA strategy, including Dex for use in THA, and complement data from studies in non-articular surgery.[3–5] Low-dose systemic Dex potentiates descending noradrenergic inhibitory controls originating from the thalamus and the locus coeruleus,

Table 1 Postoperative opioid use and opioid side-effects. There were 100 patients each in the control and OFA groups unless otherwise indicated. There were 100 patients analysed in each group during the first 24 h, which decreased after according to their discharge from the ward. Time to extubation: time from skin closure to extubation. OFA, opioid-free anaesthesia; PONV, postoperative nausea and vomiting; SAP, systolic arterial pressure; Spo_2, oxygen saturation. Data are expressed as mean (standard deviation), median [interquartile range], or number (%).

	OFA	Control	P-value
Patients who requested opioid during the first 24 h	42 (42)	61 (61)	0.007
Morphine in PACU (mg)	0 [0–3]	3 [0–6]	0.008
Time to first morphine requirement in PACU (min)	57 (30)	38 (23)	0.002
Patients who did not require morphine titration	66 (66)	50 (50)	0.02
Time to extubation (min)	19 (15)	12 (9)	<0.001
Time to PACU discharge (min)	103 (36)	106 (35)	0.45
Intraoperative maximal SAP (mm Hg)	123 (19)	137 (20)	<0.001
Intraoperative minimal SAP (mm Hg)	79 (17)	80 (16)	0.55
Intraoperative maximal HR (beats min^{-1})	75 (11)	72 (13)	0.09
Intraoperative minimal HR (beats min^{-1})	58 (9)	57 (9)	0.28
Intraoperative atropine	5 (5)	9 (9)	0.23
Oxycodone consumption (mg)			
24–48 h	0 [0–10] ($n = 91$)	0 [0–15] ($n = 99$)	0.10
48–72 h	0 [0–10] ($n = 63$)	6 [0–20] ($n = 88$)	0.08
72–96 h	0 [0–10] ($n = 20$)	6 [0–20] ($n = 60$)	0.26
Walking ability from the fourth hour	96 (96)	75 (75)	<0.001
PONV			
PACU	0	5 (5)	0.024
PACU-24 h	7 (1)	3 (1)	0.19
24–48 h	4 (4.4) ($n = 91$)	2 (2.0) ($n = 99$)	0.35
$Spo_2 \leq 94\%$			
PACU	45 (45)	66 (66)	0.003
2–24 h	7 (7)	17 (17)	0.029
24–48 h	1 (1.0) ($n = 91$)	6 (6.1) ($n = 99$)	0.07

reduces descending facilitation nociceptive processes and the spinal function of N-methyl-D-aspartate receptors, and attenuates microglia activation, giving Dex anti-hyperalgesic effects.[2,6,7] The lower opioid use in the OFA group could explain the decrease in O2 requirement. Dexmedetomidine preserved the hypercapnic ventilatory response and exhibited hypercapnic arousal similar to that observed during natural sleep.[8] The delayed time to extubation, probably related to the sedative and analgesic effects of Dex, did not influence rehabilitation. The 3 mg difference in ephedrine requirement in the OFA group must be interpreted with caution, as vasopressor use was left to the discretion of the anaesthetist. The inhomogeneous definition of hypotension/bradycardia and the different Dex infusion modalities are possible explanations for the heterogeneity of results amongst studies.[2–6] Dexmedetomidine reduces transiently cardiac output by lowering HR without significant impairment in systolic or diastolic left and right cardiac function.[9] The change in HR during Dex infusion mimics that observed in natural sleep.[10]

This study is limited by its observational nature from a single centre. However, groups were similar and the study was adequately powered for the main outcome (0.48 effect size). The use of propensity scores could have been helpful to increase the similarity between groups, but this model may still be subject to bias and imbalance between groups by unmeasured confounding variables. Except for the use of Dex instead of sufentanil, perioperative measures were conducted similarly.

In conclusion, during total hip arthroplasty performed under general anaesthesia, opioid-free anaesthesia can reduce postoperative opioid consumption, pain scores, and hospital length of stay, and can mitigate opioid side-effects when compared with an opioid-based strategy. Side-effects were limited without clinical complications.

Declarations of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.01.001.

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doi: 10.1016/j.bja.2021.01.001
Advance Access Publication Date: 3 February 2021

Role of dexamethasone in reducing postoperative pain. Comment on *Br J Anaesth* 2021; 126: 862–71

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Keywords: dexamethasone; persistent postoperative opioid use; postoperative pain; quality of recovery; rebound pain

Editor—We read with interest the recent study by Barry and colleagues,[1] in which they examined the incidence and risk factors for rebound pain after peripheral nerve block. Their study is to be commended for a number of reasons. Firstly, they highlight the significance and frequency of rebound pain after peripheral nerve block. In their single-centre retrospective cohort study that recruited 972 patients undergoing ambulatory surgery under peripheral nerve block, 482 (49.6%) experienced significant rebound pain. They defined rebound pain as the transition from well-controlled pain with a numerical rating scale (NRS) pain score of $\leq$3 to severe pain (NRS $\geq$7) within 24 h of block performance.

Awareness for the potential for rebound pain is vital, as it mandates the prescription of postoperative analgesics, including analgesics prescribed for use on discharge from hospital, to manage the rebound pain once the block wears off. These analgesic prescriptions will often include opioid analgesics, and, despite the aspirations of opioid-free analgesia and opioid-free anaesthesia protagonists,[2] regional analgesia is currently not protective against persistent postoperative opioid use (PPOU).[3] Thus, effective postoperative opioid stewardship strategies are required to mitigate harm from PPOU whenever any form of surgery is undertaken,[4] including when performed under regional or local anaesthesia.

Secondly, and equally importantly, their study highlights that i.v. dexamethasone is associated with a lower incidence of rebound pain. The benefits of i.v. dexamethasone in reducing the incidence of postoperative nausea and vomiting have been known for almost 30 yr. Research over the past decade has demonstrated that the benefits of intraoperative i.v. dexamethasone also extend to reducing postoperative pain, reducing postoperative opioid consumption, reducing sore throat associated with intubation, reducing opioid consumption and improving pain control after spinal anaesthesia, reducing postoperative fatigue, and facilitation of earlier hospital discharge (Table 1).[5–7] Consequently, i.v. dexamethasone is now specifically recommended as part of procedure-specific postoperative pain management (prospect) for procedures as disparate as Caesarean section, tonsillectomy, oncological breast surgery, rotator cuff repair, laparoscopic sleeve gastrectomy, laparoscopic hysterectomy, and laparoscopic cholecystectomy (https://esraeurope.org/prospect/). The prospect working party group is advocating bespoke guidance to aid recovery and restoration of function after different types of surgery. By methodically undertaking systematic reviews with a rigorous methodology, they are defining prospect guidance to achieve these goals.[8] This is a marked contrast to the 'pain ladder' that was devised in 1986 by the WHO for the management of terminal cancer pain, the perioperative applicability of which is now being questioned.[8,9]

The individualisation of recommendations based on surgical and patient factors is important, as there are concerns regarding the ubiquitous use of a single intraoperative dose of i.v. dexamethasone. These include increased risk of infection, poor wound healing, hyperglycaemia, and unpleasant perineal pruritus when i.v. dexamethasone is administered to awake patients.[5,10] However, there is no evidence to suggest that single-dose intraoperative dexamethasone increases the

DOI of original article: 10.1016/j.bja.2020.10.035.