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Master thesis | Original study

New insights on perioperative use of dexamethasone: A narrative review of the literature

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Abstract

Dexamethasone is already routinely used as antiemetic prophylaxis for postoperativenausea and vomiting (PONV). Some evidence has been gathered in the past years forperioperative administration of dexamethasone in other indications: analgesic effects, prevention against postoperative cognitive decline or delirium, quality of recovery, prevention of complications in cardiac surgery... We performed a review of the literature to synthesize the new evidence about dexamethasone.

Keywords: **Anesthesia, Dexamethasone, Surgery.**

Introduction

Dexamethasone is a synthetic glucocorticoid with immunosuppressive and antiinflammatory effects. The discovery of its powerful anti-emetic effects was driven by research in oncology for the treatment of chemotherapy-induced nausea and vomiting, before making its entry in anaesthesia[1]. Dexamethasone is nowadays routinely used as prevention and treatment for PONV. The actual evidence for its perioperative use is of high quality, is widely accepted and implemented in multimodal antiemetic regimens[2].

These last years, evidence is growing that dexamethasone could be used for its analgesic properties after surgery. The working mechanism and physiologic effects of corticosteroids are still incompletely understood and a matter of research. Glucocorticoids might exert their painkilling influence by inhibition of prostaglandinsynthesis, suppressing inflammatory mediators, and by direct effects on signal transmission[3-5]. Dexamethasone has in the meanwhile been implemented in several procedure-specific postoperative pain management guidelines[6-12].

As treatment of pain and PONV in modern anaesthesia has become a major priority, the future also will need to assess more interest in the quality of recovery. Thanks to its unique pharmacologic profile, dexamethasone can influence mood and decrease fatigue[13]. Tools to measure patient-centered outcomes have been developed with good validity, as the Quality of Recovery-40 questionnaire (QoR-4014. This tool evaluates different domains such as emotional state, physical comfort, pain, psychological support and physical independence by patient self-reporting[15]. Assessment of quality of recovery permits adding a patient's perspective on postoperative outcomes. Lower recovery scores have been associated with more postoperative complications and lengthier hospital stays[16].

Recent studies have investigated the potential benefits of dexamethasone for prevention of postoperative delirium (POD) or cognitive dysfunction (POCD). Delirium is an acute and fluctuating confusional state, characterized by inattention and changes in consciousness[17,18]. Delirium is associated with a higher risk for institutionalisation and mortality in elderly patients[19]. POCD is a cognitive alteration seen after surgery, that can be established by neuropsychological testing. POCD has been associated with decreased quality of life (QOL), and even increased mortality[20]. Therefore developing preventive measures are an emerging matter of interest in anaesthesiology. The aetiology remains unclear, but systemic inflammation may play a role after major surgery. Consequently, dexamethasone could potentially be

attenuating the inflammatory response, preventing those neurocognitive complications[21,22].

Huge research has been conducted lastly on the topic of steroids in cardiac surgery. Steroids have been employed trying to attenuate the inflammatory cascade after use of cardiopulmonary bypass (CBP), minimize incidence of complications and consequently decrease mortality and morbidity[23].

Dexamethasone has several benefits or indications but also potential disadvantages. They have been lately addressed in two large meta-analyses. Its administration probably has no impact on postoperative infection rates, but influence on wound healing still has to be established, especially in patients at higher risk. Also, a mild increase in glycemia was described among subjects without diabetes with, at this moment, unknown clinical significance[24,25]. Other reported side-effects include severe perineal pruritus when given before induction of anesthesia and acute development of psychiatric disorders (psychosis, mania)[26-28].

Given the recent research in the potential harmful effects of dexamethasone, and the acknowledged evidence for use of dexamethasone in PONV, we did not examine those topics in our study. Our goal was to perform a narrative review of the literature to explore new indications of the perioperative use of dexamethasone and to assess actual evidence for pain management in the adult surgical population.

Methodology

We performed a search across Pubmed, Embase and Cochrane databases for randomized controlled trials (RCT), systematic reviews and meta-analyses. The search-keywords were "perioperative", "dexamethasone", "surgery" and "anaesthesia". The search was limited to articles published in the past 10 years. The screening was performed in June 2021. Our search only included trials with adult subjects undergoing general anaesthesia. We excluded articles regarding local, locoregional and neuraxial techniques. Studies where a full text could not be retrieved were excluded. In total, 4562 studies were imported for screening, from which 1579 duplicates. 2983 studies were screened, resulting in 60 studies which were assessed for eligibility. PONV-trials were eligible when other outcomes where examined. 11 studies were excluded for reasons (e.g. small study populations, usage of local, locoregional or neuraxial techniques, withdrawal due to scientific misconduct). Finally, 49 trials and metaanalyses were integrated in our literature review. A PRISMA flowchart is presented in Fig. 1. This research was approved after ethical review (MP017970, SCONE) on May 31st, 2021. This manuscript adheres to the applicable EQUATOR guidelines.

Results

Quality of recovery

In a dose-ranging study of De Oliveira et al., including 106 patients undergoing gynaecological surgery, median QoR-40-scores were statistically significantly higher after dexamethasone administration of 0.1 mg kg-1 compared with 0.05 mg kg^{-1} or placebo, meaning a better postoperative recovery. Those effects were seen in every domain of the QoR-40 survey[29]. In a RCT by Murphy et al. including 120 patients undergoing laparoscopic cholecystectomy, higher QoR-40 scores were noted in the dexamethasone-group compared to control. The administered dose was 8 mg[13].

In another RCT with 107 subjects, the same author published the results of dexamethasone on quality of recovery in an elective cardiac surgical

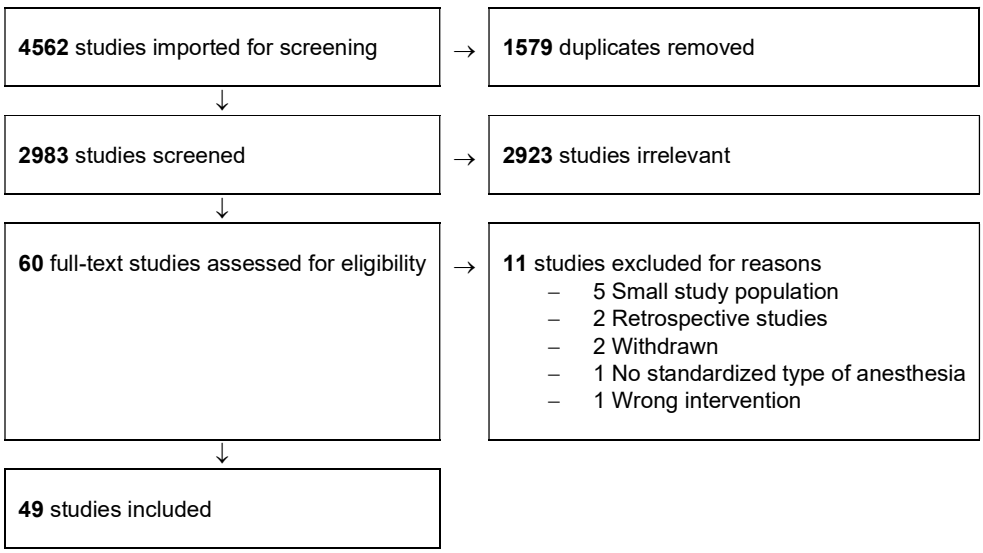

Fig. 1 — PRISMA Flow chart.

population with use of CBP. The group who received two doses of 8 mg dexamethasone had a higher global QoR-40 score compared with control group (167 vs 157, P<0.0001)[30].

A later meta-analysis of previous studies suggests that QoR-40-score improved significantly compared with placebo (MD: 14.2, CI 10.4 to 18.1; P< 0.001)[31].

An overview of RCTs related to quality of recovery are presented in Table I.

Pain

Several studies about perioperative dexamethasone have been published in the setting of gynaecological and abdominal surgery. In the previously cited RCT of De Oliveira et al. about patients undergoing gynaecological surgery, less opioids were required before discharge when dexamethasone 0.1 mg.kg^{-1} was administered compared with 0.05 mg.kg^{-1} and saline (P=0.02), but the pain scores did not differ among groups postoperatively. Time to meet discharge criteria was reduced when the higher dose of dexamethasone was administered[29]. Murphy et al. observed lower pain scores in the patients undergoing laparoscopic cholecystectomy in the dexamethasone-group (MD 10 mm, P<0.05), less pain treatment interventions (71.4% vs. 96.6% control group, P 0.001) and lower doses of opioids needed for postoperative analgesia (P<0.001). Length of stay (LOS) in hospital was also reduced in patients administered dexamethasone (P=0.003)[13]. In contrast, a RCT about use of dexamethasone in laparoscopic inguinal hernia repair with 80 subjects showed no difference in postoperative pain scores (P=0.78)[32]. In a RCT with 150 inflammatory bowel disease (IBD) patients undergoing elective abdominal surgery, either 8 mg of dexamethasone or placebo was administered. Subjects administered dexamethasone demonstrated less postoperative pain (P<0.05) compared with controls, and had a shortened LOS[33].

A RCT evaluating 80 patients undergoing breast surgery showed reduced pain scores and reduced opioid consumption postoperatively when 8 mg dexamethasone was administered[34]. In the cardiac trial of Murphy et al. no difference was seen in postoperative opioid consumption[30]. Administration of dexamethasone in the setting of lumbar discectomy surgery leaded to reduced pain during mobilisation when 16 mg dexamethasone was given compared with placebo (p= 0,005), but did not show any difference in pain at rest[35].

Numerous trials, essentially in orthopaedic surgery, have conducted their research with dexamethasone in multiple-dosing regimens. In a RCT including 120 patients undergoing total joint arthroplasty, who were administered 10 mg of dexamethasone to assess analgesia, LOS, opioid consumption and pain scores were significantly lower in the dexamethasone-group. A second dose, administered 24 hours postoperatively, resulted in additional pain control[36]. Lei et al. showed lower dynamic pain scores at 24 hours when administered two doses of 10 mg dexamethasone (P=0.002) compared with placebo in 110 patients undergoing a total hip replacement, but no decrease in opioid consumption[37]. In a later trial including 165 patients for hip surgery, a split-dose regimen of two doses of 10 mg was shown superior in decreasing postoperative pain compared with a single administration of 20 mg dexamethasone, and was associated with an increased patient satisfaction[38]. Another RCT with multiple administrations of dexamethasone in total knee arthroplasty also showed lower postoperative pain and better patient satisfaction compared to a single-dose regimen (P = 0.030).39 One RCT including 78 patients with arthroscopic knee surgery, could not demonstrate any clinically significant impact with a single-dose regimen on postoperative pain or opioid consumption[40]. Another RCT showed lower opioid consumption

Table I. — Overview of randomized clinical trials related to quality of recovery .

Study	Type	Year of publication	Procedures	Number of patients	Treatment	Median QoR40 (Range)	Comparison	Median QoR-40 control (Range)	P
De Oliveira et al. [29]	RCT	2011	Gynecological surgery	106	Dexamethasone 0.10 mg.kg^{-1}	193 (192-195)	Placebo Dexamethasone 0.05 mg.kg^{-1}	171 (160-182) 179 (175–185)	P<0.005 P=0.004
Murphy et al. [13]	RCT	2011	Laparoscopic cholecystectomy	120	Dexamethasone 8 mg	178 (130-195)	Placebo	161 (113-194)	P<0.0001
Murphy et al. [30]	RCT	2011	Cardiac surgery	117	Dexamethasone 8 mg	167 (133-192)	Placebo	157 (108-195)	P<0.0001

and lowered pain scores when dexamethasone was associated perioperatively in total knee replacement surgery.41 Several subsequent meta-analyses about total joint arthroplasties have shown comparable positive results[42-46].

A meta-analysis about analgesics for post-tonsillectomy pain, including 29 trials of which 10 about dexamethasone, reports reduced pain in the dexamethasone-group, and less rescue opioids usage when higher dosages were administered[47]. In a RCT about outcome after thyroidectomy, significant lower VAS-scores were noted in the dexamethasone-group (P=0.008)[48]. In contrast, another trial enrolling 120 patients for thyroid surgery could not demonstrate any analgesic or opioid-sparing effects[49].

Two large meta-analyses have been published, in 2011 and 2013 respectively, about the impact of dexamethasone on postoperative analgesia. The first one, including 24 RCTs, totalizing 2751 patients, demonstrated decreased pain and reduced opioid consumption when administered doses were superior to 0.1 $mg.kg^{-1}$. Furthermore, discharge times were reduced compared with placebo[50]. In the second meta-analysis including 45 studies with 5796 patients, administered doses ranged from 1.25 to 20 mg, and were compared to placebo. Patients receiving dexamethasone had significantly lower pain scores, used less opioids and rescue analgesics in the postoperative period, and had shorter PACU-stays[28].

An overview of RCTs related to pain are presented in Table II.

Outcomes in cardiac surgery

In the study of Murphy et al. about dexamethasone in cardiac surgery, no difference was seen between the two study groups in cardiac arrhythmias, duration of mechanical ventilation, LOS or incidence of complications[30].

Cappabianca et al. studied the effects of steroids in subjects undergoing cardiac surgery with CBP on mortality and morbidity. They conducted a meta-analysis of 31 RCT's with different types of steroids including dexamethasone. No influence on postoperative mortality was revealed in the dexamethasone subgroup. A significant reduction in incidence of atrial fibrillation was seen after dexamethasone administration(OR 0,56 CI 0,39-0,79, P=0.001). No statistically significant difference was seen in duration of mechanical ventilation between dexamethasone-treatment and placebogroup (MD -23 min: CI -48 to 1,4 min; P=0.06). ICU-LOS was reduced in the steroidtreated group[51].

The Dexamethasone for Cardiac Surgery (DECS)-Trial was a large multicenter RCT. The DECS-trial included 4494 patients undergoing cardiac surgery with CBP. Patients were randomized to receive $1mg.kg^{-1}$ dexamethasone or placebo. The main outcomes were incidence of death, stroke, myocardial infarction, renal and respiratory failure. The trial failed to show a difference in those outcomes (P=0.07), on behalf of the patients developing respiratory failure, with a risk reduction of 0.69 when treated with dexamethasone (3% vs 4.3%; 95% CI, 0.51-0.94; P=0.02). Secondary outcome parameters showed a lower duration of mechanical ventilation and LOS in the ICU[52]. In a post-hoc analysis dexamethasone was shown to effectively reduce the incidence of acute renal failure with need for renal replacement therapy in patients with advanced chronic kidney disease (P=0.03)[53]. Long term follow-up showed no effect on major adverse events 12 months after surgery. Cost-analysis showed reduced costs per patient attributable to reduction of respiratory failure and hospital stay[54].

In a meta-analysis totalising 16013 subjects, Dvirnik et al. studied the effects of steroids administration in cardiac surgery. The mortality in the steroid-treated group was 3.0% versus 3.5% in the placebo-group (RR 0.85; 95% CI, 0.71-1.01; P=0.07; I2=0%). Myocardial injury incidence was higher in the steroid group compared with the control group (8% vs 6,9%, RR, 1.17; 95% CI, 1.04-1.31; P=0.008; I2=0%). No subgroup analysis for dexamethasone was performed. There was a statistically significant difference in ICU- and hospital LOS[55]. These unfavourable results were supported by another meta-analysis[56].

Outcomes in non- cardiac surgery

The DeLiT-trial was a RCT that enrolled 381 subjects undergoing major non-cardiac surgery and randomized to three interventions: perioperative administration of dexamethasone (14 mg over 3 days), intensive versus conventional glycaemic control and light versus deep anaesthesia. Dexamethasone administration had no effect on morbidity or mortality[57].

In another large multicenter RCT including 1222 adults requiring major non-cardiac surgery, no difference in incidence of complications or death was seen in the first 14 postoperative days. Subjects were given dexamethasone 0.2 $mg.kg^{-1}$ two times or placebo[58].

Postoperative cognitive dysfunction

In a substudy of the DECS-trial the incidence of POCD was measured at a 1-month and 12-month interval. At 1-month, the incidence of POCD was 13.6% patients in the dexamethasone-group and 7.2% patients in the placebo-group, but the

Table II. — Overview of randomized clinical trials related to pain. Part 1.

Study	Type	Year	Procedures	Number of patients	Treatment	Control	Results publication	Side-effects / Serious adverse events
De Oliveira et al. [29]	RCT	2011	Gynaecological surgery	106	Dexamethasone 0.10 mg.kg^{-1}	Placebo Dexamethasone 0.05 mg.kg^{-1}	Reduced opioid consumption	Not evaluated
Murphy et al. [13]	RCT	2011	Laparoscopic cholecystectomy	120	Dexamethasone 8 mg	Placebo	Lower pain scores in PACU Reduced hospital length of stay Reduced opioid consumption	No complications No statistically significant difference between groups in side-effects
Tolver et al. [32]	RCT	2012	Laparoscopic inguinal hernia repair	80	Dexamethasone 8 mg	Placebo	No difference	No serious adverse events Development of 1 SSI in each groups, no other complications
Zhang et al. [33]	RCT	2021	Abdominal surgery for inflammatory bowel disease	302	Dexamethasone 8 mg	Placebo	Lower pain scores Shortened length of stay	46 Patients developed a SSI (20 (13.2%) in the dexamethasone-group, 26(17.2%) in the control group (P=0.337)) No serious adverse events
Cortès-Flores et al. [34]	RCT	2017	Breast surgery	80	Dexamethasone 8 mg	Placebo	Lower pain scores Reduced opioid consumption	No serious side effects or adverse events
Murphy et al. [30]	RCT	2011	Cardiac surgery	117	Dexamethasone 8 mg x 2	Placebo	No difference in opioid consumption	No difference in postoperative complications Higher blood glucose values in dexamethasone-group, but no statistically significant difference
Nielsen et al. [35]	RCT	2015	Lumbar discectomy	160	Dexamethasone 16 mg	Placebo	Reduced pain during mobilization	More patients treated for SSI in dexamethasone-group, but no statistically significant difference (6.5% versus 0%, P=0.13) No adverse events
Backes et al. [36]	RCT	2013	Total joint arthroplasty	120	Dexamethasone 10 mg Dexamethasone 10 mg x 2	No placebo	Lower pain scores and, continued effect with second dexamethasone dose Shorter length of stay Reduced opioid consumption	No serious adverse events One SSI in dexamethasone-group (dexamethasone 10 mg x2) 2 DVT's (1 in placebo-group, 1 in dexamethasone 10 mg x 2)
Lei et al. [37]	RCT	2018	Total hip replacement	110	Dexamethasone 10 mg x 2	Placebo	Reduced pain during mobilization Shorter length of stay	No SSI's in both groups No serious adverse events

Table II. — Overview of randomized clinical trials related to pain. Part 2.

Lei et al. [38]	RCT	2020	Total hip replacement	165	Dexamethasone 10 mg x 2 Dexamethasone 20 mg	Placebo	Lower pain scores, pain scores during mobilization lower in split-dose regimen Shorter length of stay Reduced opioid consumption	No difference in postoperative glucose values No SSI's or gastro-intestinal haemorrhages
Wu et al. [39]	RCT	2018	Total knee replacement	150	Dexamethasone 10 mg Dexamethasone 10 mg x2	Placebo	Lower pain scores, additional effect of second dose dexamethasone Reduced opioid consumption	No development of DVT or PE 3 SSI's in dexamethasone-group (1 in dexamethasone 10 mg group, 2 in dexamethasone 10 mg x2 group)
Moyano et al. [40]	RCT	2016	Arthroscopic knee surgery	78	Dexamethasone 10 mg	Placebo	No difference	No difference in adverse events
Xu et al. [41]	RCT	2017	Total knee replacement	108	Dexamethasone 10 mg x 2	Placebo	Lower pain scores Reduced opioid consumption	No SSI's or gastro-intestinal haemorrhages
Feroci et al. [48]	RCT	2011	Thyroidectomy	102	Dexamethasone 8 mg	Placebo	Lower pain scores	Temporary higher blood glucose values in dexamethasone-group No statistically significant difference between groups in complications
Doksrød et al. [49]	RCT	2012	Thyroid surgery	120	Dexamethasone 0.15 $mg.kg^{-1}$ Dexamethasone 0.30 $mg.kg^{-1}$	Placebo	No difference in pain scores, no reduced opioid consumption	Higher blood glucose values in dexamethasone-group No statistically significant difference between groups related to SSI's, delayed wound healing or dyspepsia
DVT: deep venous thrombosis, RCT : randomized controlled trial, SSI: surgical site infection, PACU: post-anesthesia care unit, PE: pulmonary embolism .								

difference was not statistically significant (RR, 1.87; 95% CI, 0.90 to 3.88; P=0.09). It also failed to demonstrate a difference at 12-month follow-up[21].

Valentin et al. showed a lower incidence of POCD when 8 mg dexamethasone was administered and combined with a light anaesthesia depth (BIS 46-55). The studied population was limited to elective surgery, and excluded cardiac and neurosurgical surgery[59]. In a RCT including 161 patients scheduled for elective cardiac surgery receiving dexamethasone preoperatively, a statistically significant reduction in the incidence of postoperative cognitive dysfunction was shown (RR, 0.43; 95% CI, 0.21 to 0.89; P = 0.02). The administered dose was 0.1mg.kg-1[60].
An overview of RCTs related to POCD are presented in Table III.

Delirium

In a substudy of the DECS-trial, the incidence of delirium was similar between the dexamethasone and placebo-group, respectively 14.2% vs 14.9% (OR = 0.95, 95% CI, 0.63-1.43). Duration of the delirium also did not differ significantly[61]. In a RCT including 93 patients undergoing coronary bypass graft a lower incidence of delirium was seen on the first postoperative day (9.3% vs. 26%, P = 0.03) when administered 8 mg of dexamethasone every 8 hours for 3 days. No significant difference was shown on the second and third postoperative day[62]. Subgroup analysis in a meta-analysis demonstrated that administration of dexamethasone in the setting of cardiac surgery with CBP was associated with

Table III. — Overview of randomized clinical trials related to postoperative cognitive dysfunction.

Study	Type	Year of publication	Procedures	Number of patients	Treatment	Control	Results	Side-effects / Serious adverse events
Ottens et al. [21]	RCT	2014	Cardiac surgery with CPB	291	Dexa-methasone 1 mg.kg^{-1}	Placebo	No reduction of incidence of POCD	Higher blood glucose values in dexamethasone-group during ICU-stay Complications not reported
Valentin et al. [59]	RCT	2016	Surgery with exclusion of cardiac- and neurosurgery	140	Dexa-meth-asone 8 mg and deep or superficial anesthesia	No placebo, deep or superficial anesthesia	Decreased inci-dence of POCD in dexa-methasone-group associated with BIS 46-55	Not reported
Glumac et al. [60]	RCT	2017	Cardiac surgery	161	Dexa-methasone 0.10 mg.kg^{-1}	Placebo	Decreased incidence of POCD in dexa-methasone-group	Not reported
ICU: intensive care unit								

Table IV. — Overview of randomized clinical trials related to postoperative delirium.

Study	Type	Year of publication	Procedures	Number of patients	Treatment	Control	Results	Side-effects / Serious adverse events
Sauër et al. [61]	RCT	2014	Cardiac surgery with CPB	737	Dexa-methasone 1 mg.kg^{-1}	Placebo	No reduction in incidence of delirium, simi-lar duration of delirium	Not reported
Mardani et al. [62]	RCT	2013	CABG	93	Dexa-methasone 8 mg every 8h for 3 days	Placebo	Lower incidence of POD on first postoperative day	No statistically significant difference between groups in surgical site infection rates Higher blood glucose values in dexa-methasonegroup

a reduction in incidence of POD (RR, 0.80; 95% CI, 0.68–0.93, P=.003)[63]. A meta-analysis published in 2019 including 5 RCT's could not show any significant difference in incidence of POCD and POD between dexamethasone-and placebo-group[22].

An overview of RCTs related to delirium are presented in Table IV.

Post-traumatic stress disorder (PTSD), Depression

In another substudy of the DECS-trial a lower prevalence of PTSD (OR, 0.23; 95% CI, 0.07–0.72; P=0.008) and depression (OR, 0.29; 95% CI, 0.11–0.77; P=0.005) has been demonstrated in the female subgroup after dexamethasone treatment compared with placebo. No statistically significant difference has been showed in incidence in PTSD and depression in the overall study population. (PTSD: OR, 0.82; 95% CI, 0.55–1.20; P=0.30; depression OR 0.92; 95% CI, 0.64–1.31; P=0.63)[64].

Postoperative ileus

Zhang et al. showed a reduction in prolonged postoperative ileus rates (22.5% vs 38.4%; P = 0.003) in the dexamethasone-group of IBD-patients undergoing abdominal surgery[33].

Quality of Life, Fatigue

In the trial of Murphy et al. about laparoscopic cholecystectomy, the degree of fatigue was significantly lower in the dexamethasone-group compared with the control-group (P= 0.005)1[3].Patients had a lower post-operative Identity-Consequence Fatigue Scale (ICFS)- score in the trial of Lei et al., meaning less tiredness[37]. Similar results were seen in the study of Xu et al[41]. Doksrød et al. reported more fatigue and disrupted sleep in the postoperative period in the higher dose dexamethasone-group compared with other groups[49]. Tolver et al. couldn't demonstrate a beneficial effect of dexamethasone on fatigue[32].

In the DREAMS-trial, a multicentred RCT examining PONV in abdominal surgery, postoperative fatigue and QOL were measured as secondary outcomes. No difference in QOL was shown between the dexamethasone and standard treatment. The research group couldn't demonstrate any difference in postoperative fatigue when dexamethasone and standard treatment-group were compared[65]. In a sub-analysis of the DeLiT-trial, similar results were reported. Steroid administration did not improve QOL at 30 days, nor did the postoperative fatigue improved significantly[66].

Discussion

Our review showed consistent findings about analgesic effects of dexamethasone on pain. Subjects who were administered dexamethasone had lower pain scores and required less opioids. Two large meta-analyses have supported the analgesic efficacy of perioperative dexamethasone. It seems that given the modest analgesic and opioidsparing effect dexamethasone surely has only a role to play in multimodal analgesic regimens. However, up until now, no optimal dosage has been determined to our knowledge. Many of the reviewed articles used a dose superior as commonly used in anti-emetic regimens. A dose-response relationship has been described in meta-analyses[28,50]. The anti-emetic and adjunctive analgesic effect of dexamethasone, probably led to the shorter PACU (post-anesthesia care unit)-and hospital stays, as revealed in several trials.

Evidence for analgesic efficacy has mainly been gathered in abdominal, gynaecological, orthopaedic and ear-nose-and throat (ENT) surgery. This limited evidence restricts potential generalization to other surgery types. Little to no research has been published on eventual analgesic effects of dexamethasone in thoracic and cardiac surgery without adjunction of locoregional analgesia techniques. As major and complex surgery is often associated with epidural analgesia, this complexifies potential data collection. A possible path for future research is the study of multiple-dose regimen compared to single-dose administration. Numerous trials have shown promising results in multiple drug administrations, with additional benefit, even 24h after the surgical intervention.

The analgesic effects of dexamethasone are probably explained by inhibition of cytokine-production and phospholipase-A2, decreased leukocyte function and reduced inflammatory mediator release by endothelial cells[29,40].

In the present study, we found arguments for a superior quality of recovery with the perioperative use of dexamethasone. Since our search only found 3 trials, conclusions are restricted by the limited research on patient-centered outcomes about dexamethasone. Using the QoR-40-questionnaire permits to add the patient subjective experience to our trials, and enables us to quantify that recovery process. This enhanced recovery may be explained by a sense of well-being produced by dexamethasone[13]. In addition, dexamethasone may exhibit an influence on depressive symptoms[64]. Effect of dexamethasone on postoperative fatigue and QOL seems to be less clear. Our analysis showed inconclusive results for those two outcomes. One study revealed potential disrupted sleep and more fatigue in the dexamethasonegroup[49].

The most evidence about dexamethasone on outcomes in cardiac surgery has been retrieved from

the DECS-trial. Unfortunately, no difference has been demonstrated in incidence of major adverse events or survival. Potential reported benefits were the reduced rate of postoperative respiratory failure, related LOS and associated costs in the ICU-ward[52,54]. However, in 2015 the results of the SIRS-trial were published, showing no significant effect of methylprednisolone on morbidity and mortality[67]. Later, in the meta-analysis of Dvirnik et al. an unclear effect had been showed on mortality, and an increased incidence of myocardial injury was reported in the steroid-treated group. Therefore, steroids are not recommended anymore in European guidelines on CBP in adult cardiac surgery[68]. Our review showed similar result tendencies in noncardiac surgery, and as such, no data supports dexamethasone administration to prevent complications and death in major surgery.

Limited evidence is available for pharmacological prevention of POD and POCD with dexamethasone. POD is a complex and multifactorial alteration of the mental state, and therefore management should be based on several steps. Risk estimation, perioperative neuromonitoring, delirium screening, nonpharmacological measures and treatment of underlying causes of delirium are recommended to improve outcome. Pharmacological measures have been questioned in the past[18]. Based on our results, dexamethasone cannot be recommended for prevention of POD because of conflicting findings. Likewise, administration of dexamethasone did not seem to reduce the incidence of postoperative cognitive dysfunction. Our review is restricted by the fact that most of the studies were carried out in cardiac surgery setting. More trials with large study populations will be needed to discover any eventual beneficial effect of dexamethasone on POD and POCD. Furthermore, a better understanding of the underlying pathophysiological mechanisms of those disorders is needed.

Our review is limited by heterogeneity by assessment of trials with different primary outcomes, surgery type, timing of intervention and various dexamethasone dosage administrations. Also, several number of trials excluded patients with chronic use of steroids and thus evidence for use may be limited in this population. In a precautionary principle, attention should be paid before dexamethasone administration in high-risk patients, like patients with diabetes, myocardial ischemia, immunosuppression and chronic use of steroids. Some of the reviewed trials reported higher glucose values in dexamethasone-treated groups, but no proof was demonstrated for increased surgical site infection rate or other adverse effects.

Conclusions

To conclude, administration of dexamethasone reduces postoperative pain and opioid consumption after surgery, has a beneficial impact on patient-reported outcome measures and reduces length of stay. However, no clear beneficial effects have been shown for prevention of postoperative delirium or cognitive dysfunction. Use of dexamethasone in cardiac and major surgery setting for prevention of complications remains controversial.

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