Dexamethasone as analgesic in different types of gynecologic surgery – A literature review

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Abstract

Background: **Dexamethasone is a glucocorticoid and is widely used for postoperative nausea and vomiting (PONV). Recent studies and subsequent guidelines also suggest a role as an analgesic. Dexamethasone as an analgesic has been studied with varying degrees of success in different types of surgery with intravenous doses ranging from 4 mg to 80 mg. The procedure specific postoperative pain management (PROSPECT) guidelines for elective cesarean sections, laparoscopic hysterectomy and oncologic breast surgery all recommend the use of dexamethasone as an analgesic in a multimodal pain regimen, however a particular dose is not mentioned.**
Objective: **To provide a literature review of the use of dexamethasone as an analgesic and at what dosage it has been studied in elective cesarean sections, gynecological laparoscopy and oncologic breast surgery.**
Methods: **The Embase, PubMed, and Cochrane databases were searched for randomized controlled trials published between 2000 and 2021.**
Results: **A total of thirty-four articles were found. Fourteen about elective cesarean section, Thirteen concerning gynecologic laparoscopy and seven regarding oncologic breast surgery. Literature review demonstrated that during elective cesarean section the intravenous (IV) doses ranged from 4 mg to 16 mg. The most investigated IV dose was 8 mg, but overall studies showed conflicting results concerning pain scores and analgesic use. In gynecologic laparoscopy the IV dose ranged from 4 mg to 15mg and again 8 mg was the most frequently studied dose. The IV dose of dexamethasone in oncologic breast surgery ranged from 8 mg to 24 mg. Also in these studies the results were conflicting. In addition, dexamethasone was used as an adjunct to locoregional blocks (perineural use): the transversus abdominis block (TAP) in cesarean section, the serratus anterior plane block (SAP) and the paravertebral block (PVB) in oncologic breast surgery.**
Conclusion: **This literature review provides an overview of the use of dexamethasone in elective cesarean section, gynecologic laparoscopic surgery and oncological breast surgery. Three routes of administration were examined: intravenous, perineural and intraperitoneal. IV 8 mg dexamethasone was the most studied dosage but there were mixed results. Based on this literature review we cannot draw any conclusions regarding the analgesic dose. Further research, with more qualitative RCT's and systematic reviews with meta-analysis are needed.**

Keywords: **Dexamethasone, Analgesia, cesarean section, cesarean section, gynecologic surgery.**

Introduction

Post-operative pain has many adverse effects on the patient. First, it has a significant impact on the psychological well-being. It also causes stress and sleep disturbances, which slows down postoperative recovery[1]. In addition, there is an increased morbidity because of changes in normal physiology[2]. Inadequately treated postoperative pain increases medical costs for the patient and the hospital[3]. Due to acute postoperative pain, there

is also a greater need for strong rescue analgesia with opioids. The use of opioids to treat acute pain is accompanied by well know side effects such as ileus, PONV, respiratory depression, etc[4]. If we can reduce their use we possible avoid these side effects. Finally adequate treatment of postoperative pain is important to prevent the development of chronic pain[5]. To address these problems, the multimodal pain policy was developed. The aim of this is, on one hand, to obtain optimal analgesia and, on the other hand, to limit the side effects of

each analgesic[2]. Examples of this multimodal pain regimen are the PROSPECT guidelines.

Dexamethasone was first described as an anti-emetic in chemotherapy[6]. It has subsequently found its way into anesthesia as PONV prophylaxis. An IV dose of 4-10mg is used in the literature[7]. In addition, several studies have examined the analgesic and anti-inflammatory effect of dexamethasone after surgery, mainly in laparoscopic cholecystectomy[8], tonsillectomy[9], orthopaedic surgery[10] and dentistry[11,12].

The analgesic effect of dexamethasone is multifactorial and theoretically deducible from its pharmacological effect[13]. A subset of surgical procedures in which dexamethasone is administered is gynecologic surgery. The PROSPECT guidelines recommend its prophylactic use for PONV and as an adjuvant analgesic but they do not provide guidance on the dose. In this article we want to examine how and at what dosage dexamethasone is used as an analgesic in three specific interventions, namely elective cesarean sections, gynecological laparoscopy and oncological breast surgery.

Methods

The Embase, PubMed, and Cochrane databases were searched for randomised controlled trials published between 2000 and 2021 in the English literature. The search terms we used were (gynecologic surgery OR breast surgery OR cesarean section OR gynecologic laparoscopy) AND (postoperative pain OR analgesia OR anesthesia) AND (dexamethasone). Relevant articles were selected from the reference lists of systematic reviews and meta-analyses. Records were selected based on the title and abstract. All randomised controlled trials (RCT's) were subjected to a risk of bias analysis with the use of the COCHRANE ROB2 assessment tool (see online supplement) (Figure 1).

Results

Elective cesarean section

Fourteen articles were retained on the use of dexamethasone. An overview can be found in Table I and table A in the online supplements. These articles can be divided into three groups: IV use, adjuvant use in transverse abdominis block (TAP) and adjuvant use in local wound infiltration. First, ten studies looked at the analgesic effect of an IV bolus of dexamethasone at a dose of 4 to 10 mg.

Literature review showed that 8 mg dexamethasone was the most studied IV dosage, with nine studies in total. Shahraki et al[14] found in 60 patients a significantly lower pain score
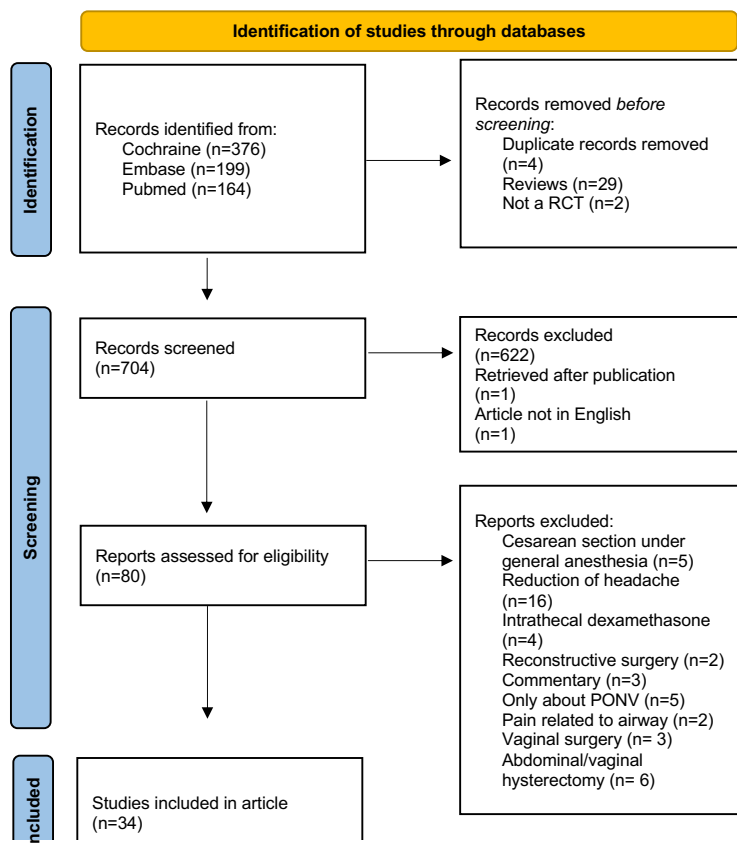

Fig. 1 — PRISMA flow diagram identification of studies.

Table I. — Elective cesarean section.

Author; Study type; Year	Patients included	Dexamethasone dose protocol; timing administration	Result	Interval pain score	Basline analgesics	Rescue
Shahraki et al.[14]; RCT; 2013	60	IV 8mg dexa vs placebo; After umbilical cord clamping.	Significant lower VAS score and significant lower morphine use in dexa group.	15min, 30min, 1h, 2h, 4h, 6h, 12h, 18h, 24h	Epidural anesthesia with bupivacaine 0,5% and 4mg morphine.	Morphine IV
Jaafarpour et al.[15]; RCT; 2008	80	IV 8mg dexa vs placebo; After umbilical cord clamping.	Significant lower VAS and significant lower post-op analgesia use in dexa group.	3h, 6h, 24h	Spinal lidocaine 5%, diclofenac or pethidine.	Diclofenac or pethidine.
Shalu et al.[16]; RCT; 2017	60	IV 8mg dexa vs placebo; Imediatly after spinal anesthesia.	Significant lower VAS from 1h post-op. Significant longer sensory block. Significant longer time to rescue analgesia in dexa group.	30min, 1h, 2h, 4h, 6h, 8h, 12h, 18h, 24h	Spinal bupivacaine 0,5%	Tramadol
Ituk et al.[18]; RCT; 2018	52	IV dexa 8mg vs placebo; After umbilical cord was clamped	No difference of 8mg dexa on total opioïd consumption or NRS	6h, 12h, 24h	Spinal bupivacaine, morphine 200μg and fentanyl 25μg , IV ketorolac	Morphine (NRS >6) or oxycodon 5mg (NRS <6)
Mehdiratta et al.[19]; RCT; 2021	47	IV dexa 8mg vs placebo; After spinal anesthesia	No difference in total opioïd consumption, pain scores (NRS) or time to first analgesic request.	2h, 24h, 48h	Spinal anesthesia with bupivacaine + 15 μg fentanyl + 150 μg morphine, IV naproxen+paracetamol;	Fentanyl
Wu et al.[17]; RCT; 2006	120	IV 8mg dexa vs 4mg dexa (+droperidol 0,625mg) vs placebo; Before skin incision	Only reported pain scores, Significant lower pain scores (start after 6h) in 8mg dexa group.	0h, 3h, 6h, 24h	Spinal anesthesia with bupivacaine + morphine 200 μg	Diclofenac IM
Nortcliffe et al.[21]; RCT; 2003	90	IV dexa 8mg vs placebo; In recovery room.	No difference in pain score (VAS) Secondary end-piont	0h, 3h, 6h, 12h, 24h	Spinal anesthesia with bupivacaine + 200 μg morphine + 10 μg fentanyl, diclofenac	Paracetamol +codeine
Selzer et al.[22]; RCT; 2020	108	IV 8mg dexa vs placebo; Before arrival in OR	No difference in pain score (NRS) or total opioïd consumption. Secondary endpoint	0h, 3h, 6h, 24h, 48h	Spinal anesthesia with bupivacaine + 200 μg morphine + 20 μg fentanyl, Ibuprofen or ketorolac	Oxycodon +paracetamol
Cardoso et al.[23]; RCT; 2013	70	IV 10mg dexa vs placebo; Immediately prior to surgery	Significant lower number of patiënts with pain in dexa group.	1h, 2h, 3h, 6h, 12h, 24h	Spinal anesthesia with hyperbaric bupivacaine + morphine 6 μg, ketoprofen, dipyrone	Tramadol
Gupta et al.[24]; RCT; 2019	90	PN 4mg dexa with TAP vs Ropivacain and TAP block placebo; After skin closure	Significant lower opioïd consumption and VAS somatic (superficial pain) and VAS visceral (deep, generalised pain) when dexa added to TAP.	1h, 2h, 4h, 8h, 12h, 24h	Spinal anesthesia with bupivacaine and fentanyl, Paracetamol, TAP	Tramadol

Author; Study type; Year	Patients included	Dexamethasone dose protocol; timing administration	Result	Interval pain score	Basline analgesics	Rescue
Liu et al.[25]; RCT; 2020	80	PN 5mg dexa with TAP block vs TAP block alone; After skin closure	Significant lower use of PCIA and VAS score in TAP block with 5mg dexa.	2h, 6h, 10h, 12h, 14h, 16h, 20h, 24h	Spinal anesthesia with ropivacaine 0,5%, TAP	Post-op PCIA (tonoforphan, dextrozine, dexmedetomidine)
Akkaya et al.[26]; RCT; 2014	40	PN 8mg dexa with TAP block vs TAP block with placebo; After skin closure	Significant lower NRS and opioïd consumption (tramadol) when dexa was added to TAP block.	1h, 2h, 4h, 8h, 16h, 24h	Spinal anesthesia with bupivacaine 0,5%, TAP	Tramadol
Maged et al.[27]; RCT; 2017	120	SC 16mg dexa wound infiltration vs IV 16 mg dexa vs placebo; IV and SC after skin closure	Significant lower VAS and opioid (morphine) consumption in IV vs placebo group and in SC vs placebo group. Significant lower morphine use in SC vs IV dexa group. More nausea and vomiting in last group.	1h, 4h, 6h, 8h, 12h, 24h	Spinal anesthesia with 10mg of 0,5% bupivacaine and 20 µg fentanyl	Morphine
Edom-wonyi et al.[20]; RCT; 2019	120	IV tramadol 100mg vs IV 8mg dexa; After skin closure	Significant lower opioid consumption and lower VAS score in Tramadol group. More nausea and vomiting with tramadol but not significant.	10min, 30min, 1h, 2h, 3h, 4h, 6h, 8h, 24h	Spinal anesthesia with bupivacaine and wound infiltration with bupivacaine 0,1%	Pentazocine

and significantly lower morphine consumption when 8 mg of dexamethasone was administered after cord clamping. Spinal anesthesia was performed with bupivacaine 0.5%. Jaafarpour et al[15] demonstrated, in a study population of 80 patients, a significantly lower pain score three, six and twenty four hours postoperative and lower postoperative consumption of diclofenac and pethidine in the 8 mg of dexamethasone group versus placebo. Shalu et al[16] also found a significantly lower pain score at all times and longer time to first analgesic need in a group of 60 patients chen comparing IV 8 mg dexamethasone versus IV placebo. No opioids were used in spinal anesthesia. In the RCT by Wu et al[18], analgesia was a secondary endpoint. Here, in 120 patients, the mean visual analogue pain score (VAS) was significantly lower in the period six to twenty-four hours postoperative when 8 mg dexamethasone was compared to 4 mg dexamethasone and to placebo. Between time point zero and six hours postoperatively there was no significant difference. Spinal anesthesia consisted of bupivacaine and 200 micrograms (µg) of morphine. Five studies could not demonstrate a significant effect. Two articles had analgesia as a secondary endpoint. Three studies had analgesia as the primary endpoint. Ituk et al[18] studied 8mg dexamethasone versus placebo. They could not demonstrate a significant difference with respect to pain scores, total opioid consumption or time to need for additional analgesia when using a multimodal postoperative analgesia regimen. Mehdirata et al[19] studied IV 8 mg dexamethasone versus placebo in a population of 47 patients. Spinal anesthesia consisted of bupivacaine, 15 µg fentanyl and 150 µg morphine. They could not discern a difference in pain score or total opioid consumption. In the study by Edomwoyi et al[20], 120 patients were randomized after elective cesarean section

under spinal anesthesia with intrathecal hyperbaric bupivacaine 0.25%, the wound was infiltrated with bupivacaine 0.1%. In addition, either IV 8 mg of dexamethasone or IV 100 mg of tramadol was administered. It was found that bupivacaine wound infiltration with IV tramadol provided a significantly stronger analgesic effect. There was a significant lower VAS score at 30 minutes and 60 minutes postoperatively but this disappeared after 2 hours. There was also a significant lower total pentazocine consumption over the course of 24 hours. However, there was no difference in time to first analgesia request. There were two studies that examined the IV administration of 8 mg of dexamethasone for the prevention of PONV where analgesia was a secondary endpoint. In a study population of 90 patients, Nortcliffe et al[21] could demonstrate no difference in pain score when dexamethasone 8 mg was administered in the recovery room. Spinal bupivacaine, 200 μg morphine and 10 μg fentanyl were used. Selzer et al[22] were unable to demonstrate any effect of IV 8 mg dexamethasone when administered preoperatively in a group of 108 patients on the pain score or opioid consumption. The spinal anesthesia consisted of bupivacaine, morphine and fentanyl.

Cardoso et al[23] randomised 70 patients to receive either 10 mg of dexamethasone or a placebo before incision IV. Spinal anesthesia was performed with bupivacaine and 60 μg of morphine. They found a significantly lower number of patients with pain starting six hours postoperative, twelve hours postoperative and lasting to the end of follow-up at twenty-four hours. No data on postoperative opioid consumption was obtained.

Dexamethasone has also been studied as an adjuvant to transversus abdominis plane (TAP) block. Three studies looked at this in more detail. Gupta et al[24] was the largest RCT with 90 patients in which 4 mg of dexamethasone or a placebo was added to ropivacaine for the TAP block. Spinal anesthesia was performed with bupivacaine and fentanyl. They found a significantly lower opioid consumption and lower pain scores for deep and superficial pain at eight, twelve and twenty-four hours postoperatively. Finally they found a significant longer time to first rescue analgesic need. Liu et al[25] compared 5 mg of dexamethasone with placebo when added to ropivacaine before TAP block in a group of 80 patients. They also found a significantly lower need for patient controlled IV analgesia (PCIA) and a significantly lower pain score starting two hours post-operative and lasting until sixteen hours postoperative. Akkaya et al[26] studied 8 mg of dexamethasone versus placebo as an adjuvant to levobupivacaine in TAP block. In two randomized groups, 8 mg of dexamethasone significantly reduced tramadol consumption. It also significantly reduced pain scores starting from two hours postoperative and lasting until twenty-four hours.

Finally one studie compared the IV use of dexamethasone with its local use. Maghed et al[27] used the highest IV dose we found in this literature review. They studied the difference between subcutaneous (SC) and IV use of 16 mg dexamethasone in a group of 120 patients. No local anesthetic was used at the SC infiltration. They found a significantly lower pain score and lower morphine consumption in the patients with SC infiltration of dexamethasone.

Gynecologic laparoscopy

A total of thirteen studies were identified in which dexamethasone was studied as an analgesic in gynecological laparoscopy. An overview can be found in Table II and Table B in the online supplements.

Three studies examined the IV use of dexamethasone with pain scores as the primary endpoint. Seven studies examined this with pain not as primary endpoint but also reported pain scores and/or opioid consumption. The most commonly used IV dose was 8 mg, the doses ranged from 4mg to 15mg.

Kassim et al[28] reviewed 0.1 mg/kg IV dexamethasone and 60 mg duloxetine versus placebo in 75 patients undergoing exploratory gynecological laparoscopy for infertility with pain scores as primary endpoint. They could not demonstrate any significant difference in pain score or opioid consumption when dexamethasone alone was compared to placebo. Thangaswamy et al[29] studied 55 patients undergoing laparoscopic hysterectomy under general anesthesia. They demonstrated significantly lower postoperative fentanyl use and longer time to first analgesic requirement in favor of 8 mg dexamethasone over 4 mg dexamethasone and placebo when administered 2 hours before induction. They could not demonstrate lower pain scores. The last study to examine dexamethasone with pain scores as the primary endpoint was that by Jokela et al[30]. 129 patients undergoing laparoscopic hysterectomy were given a placebo, 5 mg, 10 mg or 15 mg of dexamethasone intravenously at induction. They found no difference in pain scores but a significantly lower postoperative oxycodone consumption with 15 mg.

Corcoran et al[31] studied the effect of 4 mg IV dexamethasone on cellular and metabolic components of the immune system. The study

Table II. — Gynecologic laparoscopy.

Author; Study type; Year	Patients included	Dexamethasone dose protocol; timing administration	Result	Interval pain score	Basline analgesics	Rescue
Lee et al.[33]; RCT; 2003	168	IV 8mg dexa vs placebo; Immediately before induction.	No significant difference between groups. Only avarage VAS score (no analgesic requirement was documented).	Only average pain-scores	Ketorolac	Not reoprted
Thangaswamy et al.[29]; RCT; 2009	55	IV 8mg dexa vs IV 4mg dexa vs placebo; 2 h before induction	No lower VAS at rest or at movement, significant longer time to first analgesic requirement and opioïd sparing effect (fentanyl) when 8mg dexamethasone is used.	30min, 1h, 2h, 4h, 8h, 12h, 24h	Fentanyl	PCIA
Jokela et al.[30]; RCT; 2009	129	IV 5mg dexa vs IV 10mg dexa vs IV 15mg dexa vs placebo; At induction	No difference in VAS. Significant lower oxycodon use with dexa 15mg an dexa 10mg vs placebo in first 2h.	2h, 4h, 6h, 8h, 12h, 24h	Oxycodon	PCIA
Kassim et al.[28]; RCT; 2018	75	IV dexa 0,1mg/kg + duloxetine vs only duloxetine; 2h preoperative	No difference in VAS if dexa 0,1mg/kg was added to duloxetine. Non significant difference in total pethidin use. Non significant difference in time to first analgesic requirement.	30min, 1h, 2h, 6h, 12h	No standard post-op analgesia reported.	IM pethidine 0.5 mg/kg
Nouri et al.[38]; RCT; 2021	130	IP 16mg dexa vs placebo; During surgery	Significant lower VAS (shoulder pain), significant lower opioïd use.	0h, 2h, 6h, 12h, 24h	No standard post-op analgesia resported	Pethidine 50mg
Chu et al.[32]; RCT; 2008	400	IV 5mg dexa vs placebo; 15min after induction	No difference in VAS and total analgesic use. Study about PONV	0h, 2h, 24h	No standard post-op analgesia resported	Ketorolac and meperidine
Asgari et al.[39]; RCT; 2012	63	IP 16mg dexa vs placebo; End of surgery	Significant lower VAS and opioïd consumption when 16mg dexa administered IP. No complications (wound infections, delay in wound healing)	0h, 2h, 4h, 8h, 12h, 24h	No standard post-op analgesia resported	Pethidine
Ismail et al.[40]; RCT; 2019	80	IV 8mg dexa or IP 8mg dexa; End of surgery	Non significant lower VAS, Pethidine use and time to first analgesic requirement in 8mg dexa IP group	0h, 1h, 4h, 8h, 12h, 24h	Paracetamol	Pethidine
Corcoran et al.[31]; RCT; 2017	32	IV 4mg dexa vs placebo; After induction	No difference in VAS score when 4 mg dexa was added. Pain was not a primary endpoint.	At discharge of PACU	Paracetamol, ibuprofen orally	Oxycodone 5–15 mg
Kasagi et al.[37]; RCT; 2013	120	IV 8mg dexa vs droperidol vs naloxone vs combination of three; Immediately before induction	No difference in NRS, Total dose of Fentanyl. Study about PONV.	3h, 6h, 12h, 20h	Fentanyl +flurbi-profen	PCIA fentanyl

Author; Study type; Year	Patients included	Dexamethasone dose protocol; timing administration	Result	Interval pain score	Basline analgesics	Rescue
Maddali et al.[34]; RCT; 2003	120	IV 8 mg dexa + metoclopramide vs IV 8mg dexa + ondansetron vs placebo; 2-3 min before induction	No significant difference in pain scores and requirements for rescue analgesics. Study for PONV.	1h, 2h, 3h, 4h, 5h, 6h, 8h, 10h, 12h, 16h, 20h, 24h	Diclofenac at end of surgery	Propacetamol.
Yuksek et al.[35]; RCT; 2003	60	IV 8mg dexa vs ondansetron vs placebo; 2 min before induction	No difference in VAS, in time to first rescue analgesic. Study for PONV.	1h, 2h, 3h, 6h, 9h, 12h, 15h, 18h, 21h, 24h	No standard post-op analgesia res-ported	Epidural an-algesia with Morphine + fentanyl
Pan et al.[36]; RCT; 2008	60	IV 8mg dexa + ondansetron 4mg vs placebo; At induction.	No difference in postdischarge analgesic requirement or VAS scores. Study for PONV.	0h, 8h, 24h, 48h, 72h, 96h, 120h	Ibuprofen or oxy-codone	Fentanyl

was conducted on a total of 32 patients who underwent one of the following laparoscopic procedures: hysterectomy, salpingectomy, excision of endometriosis or ovarian cystectomy. They could not show any difference in reported pain scores. Chu et al[32] studied the effect of 5 mg IV dexamethasone on PONV in 400 patients undergoing laparoscopically assisted vaginal hysterectomy. Secondary endpoints, pain score and analgesia, were not significantly different between the 2 groups. Five studies[33-37] examined 8 mg IV dexamethasone in the context of PONV but also reported pain scores and/or analgesia consumption. No study could demonstrate a significantly lower pain score or lower analgesic consumption.

In addition, we found two studies that studied the intraperitoneal (IP) use of dexamethasone as an analgesic. Nouri et al[38] included 130 patients undergoing laparoscopy for hysterectomy, myomectomy, salpingectomy or diagnostic laparoscopy under general anesthesia. At the end of surgery, 16 mg of dexamethasone or a placebo was administered intraperitoneal. A significantly lower pain score for shoulder pain and postoperative consumption of pethidine were found in the group receiving dexamethasone. Asgeri et al[39] found similar results in 63 patients who, after randomization, received IP 16 mg dexamethasone or placebo at the end of surgery. In addition, they reported no higher incidence of complications (wound infections, delayed wound healing) after 24 hours.

Finally, Ismaïl et al[40] compared the IP administration of 8 mg of dexamethasone with the IV use of the same dose in 80 patients. This study was designed to investigate the effect on PONV. Pain score and analgesia consumption were secondary endpoints. No significant difference

could be shown between both groups for pain scores and pethidine consumption. No control group was used so they could not conclude whether 8 mg of dexamethasone, either IV or IP had an analgesic effect.

Oncological breast surgery

We identified a total of seven articles that studied the use of dexamethasone in oncological breast surgery. An overview is given in Table III and table C in the online supplements.

Five articles were included that examined the IV use, the dose ranged from 8 mg to 24 mg. The most commonly studied IV dose was 8 mg in three studies. Gomez-Hernandez et al[41] compared 8 mg with placebo in 70 patients who underwent unilateral mastectomy with axillary dissection. Dexamethasone was administered just before incision of the skin. Their baseline analgesia was ketorolac. Rescue analgesic was tramadol. Significantly lower pain score and postoperative lower analgesics were used in the 8 mg group. Cortés-Flores et al[42] studied 8 mg of dexamethasone versus placebo in a group of 80 women undergoing partial mastectomy with or without axillary gland removal. It was administered intravenously 1 hour before induction. Postoperatively, systematic ketorolac was provided; Rescue analgesia was IV morphine. After administering 8 mg of dexamethasone, they found a significantly lower pain score and significantly lower morphine consumption. Steinthorsdottir et al[43] compared 8 mg with 24 mg of dexamethasone in a group of 130 patients. Dexamethasone was administered immediately after induction. Their postoperative pain protocol consisted of local wound infiltration with a local anesthetic and IV paracetamol; rescue

Table III. — Oncologic breast surgery.

Author; Study type; Year	Patients included; Surgery Type	Dexamethasone dose protocol; timing administration	Result	Interval pain score	Basline analgesics	Rescue
Gomez-Hernandez et al.[41]; RCT; 2010	70; Unilateral mastectomy with axillary dissection	IV 8mg dexa vs placebo; Before skin incision.	Significant lower VAS and post-operative analgesic need in 8mg group.	0h, 6h, 12h, 24h	Ketorolac	Tramadol
Cortés-flores et al.[42]; RCT; 2017	80; Partial mastectomy with/without axillary gland removal	IV 8mg dexa vs placebo; 1h before induction.	Significant lower painscores and total analgesic use.	1h, 6h, 12h, 24h	Ketorolac	Morphine
Steinthorsdottir et al.[43]; RCT; 2020	130; Unilateral mastectomy with or without axillary dissection	IV 24mg dexa vs 8mg dexa; Immediately after induction	Primary looked for effect on skipping PACU. Pain was secondary endpoint. No difference in pain scores. (no total analgesic use reported)	At extubation, every 15 min till arrival at PACU or ward.	Paracetamol +Wound infiltration	Paracetamol and ibuprofen, opioïds
Hval et al.[44]; RCT; 2007	100; Mastectomy + sentinel or axillary gland removal	IV 16mg dexa vs placebo; Immediately after induction	No significant differences in pain scores and total rescue analgesic use.	1h, 2h, 3h, 4h, 24h, 72h	Fentanyl + woundinfiltration	fentanyl (first 4 hours), Oxycodone
Bakeer et al.[45]; RCT; 2019	50; Modified radical mastectomy	IV 8mg dexa with PVB vs IV placebo added to PVB; When PVB was administered	Significant lower painscores, significant lower total morphine use in dexa 8mg group. Significant longer duration of PVB.	2h, 6h, 12h, 24h	Fentanyl +PVB	Morphine
El Mourad et al.[46]; RCT; 2018	90; Modified radical mastectomy	PN 4mg dexa + PVB vsPVB + placebo vs PVB + Ketamin; Before induction	Significant lower total analgesic use and longer time to first rescue analgesic. Significant difference in pains core from 6u post-op.	0h, 2h, 6h, 12h, 18h, 24h	Paracetamol	Morphine
Kumar et al.[47]; RCT; 2020	60; Modified radical mastectomy	PN 8mg dexa + SAP block vs SAP block + placebo; After induction	Significant lower pain scores, but clinicaly limited. Significant longer time to first rescue analgesic. No difference in total analgesic use.	0h, 1h, 2h, 6h, 12h, 24h	Paracetamol	Diclofenac and tramadol

analgesia was ibuprofen and opioids. They looked at whether the high dose of dexamethasone had an effect on the standardized discharge criterion scoring system (Danish Society of Anaesthesiology and Intensive Care Medicine [DASAIM] score, a modified version of the Aldrete discharge score), including pain scores. They could not detect an effect on the discharge score or the pain scores. Total analgesic consumption was not considered. Hval et al[44] studied 16 mg of dexamethasone with placebo in a group of 100 women undergoing mastectomy with sentinel or axillary gland removal.

Dexamethasone was administered immediately after induction. At the end of surgery, the wound was infiltrated with a local anesthetic, and the patient received IV paracetamol, rofecoxib and fentanyl. Fentanyl was used as a rescue analgesic in the recovery room, oxycodone after discharge. They could not show any effect in the first 4 hours on pain scores and on total analgesic use. There was only a significant decrease in pain scores with movement in the period between 4 hours and 72 hours postoperatively. The last study to examine the IV use of dexamethasone was by Bakeer et al[45].

In a group of 25 patients who underwent modified radical mastectomy under regional anesthesia with a paravertebral block (PVB), they looked at the effect of 8 mg of dexamethasone with a placebo. It was administered IV at the time the PVB was administered. In case of breakthrough pain, the patient received IV morphine. They were able to show a significantly lower pain score, a significantly longer duration of action of the PVB and a lower total opioid use.

Two articles studied the PN use, here the dose ranged from 4 mg to 8 mg. El Mourad et al[46] studied the effect of 4 mg of dexamethasone or ketamine versus placebo as an additive to bupivacaine for PVB. This was done in a group of 90 patients who had to undergo a modified radical mastectomy. The PVB was administered just before induction. Basic analgesia consisted of systematic paracetamol and morphine was administered in case of breakthrough pain. There was a significantly lower pain score from 6 hours postoperatively in the dexamethasone group versus placebo. In this group, there was also a significantly lower need for morphine and a longer duration of action of the PVB. After 18 hours, the PN ketamine group had the lowest pain scores. Kumar et al[47] compared 8 mg of dexamethasone with placebo as an additive to the serratus anterior block (SAP) in 60 patients undergoing modified radical mastectomy. Here, the SAP was administered after induction. Postoperatively, paracetamol was systematically administered and if necessary, the patients received diclofenac and tramadol. They demonstrated a significantly lower pain score and longer time to administration of rescue analgesia. There was no difference in total analgesia consumption.

Discussion

Pain is subjective and multifactorial. It is difficult to objectively measure a significant improvement on pain scores. This can partly be overcome by looking at different outcome parameters at the same time, such as pain scores, analgesic consumption, time to need for additional analgesia, ... It is also possible to measure for example the effect on the Quality of Recovery (QoR) score but pain is only a part of this. Furthermore, it is difficult to distinguish between a statistically significant difference and a clinically significant difference. Several attempts have been made to answer this question. The results were diverse and reductions of 10-40% in VAS on a scale of 100mm were considered clinically significant[48-52].

All studies we found looked at whether there was a statistically significant difference after the use of dexamethasone. When one can speak of a clinically

significant difference remains a point of discussion. All studies included here measured one or more of three outcome parameters (pain scores, analgesic consumption, time to first analgesic need) to study the effect of dexamethasone.

Elective cesarean section

Prospect guidelines recommend the use of dexamethasone to prevent PONV and as a co-analgetic, but no dosage is mentioned[53]. In this literature study we try to get a better picture of how and in what dosage dexamethasone as an analgesic has been studied in the literature. In elective cesarean section lower pain scores contribute to the recovery of the woman and the further development of the mother-child relationship. In addition, young mothers often want to start breastfeeding. Therefore it is necessary that they experience as few side effects as possible from the chosen pain policy. Here, we discuss the studies that examined the intravenous, perineural and subcutaneous use of dexamethasone. We describe the studies according to the dosage that was used. It is notable that throughout all studies there is a different timing of administration of dexamethasone, a variable protocol for spinal anesthesia (with or without an opioid) and a great difference in postoperative pain protocol. Important to note is that also intrathecal dexamethasone has been studied in the literature but we do not describe it here.

Nine studies analyzed the IV use of 8 mg dexamethasone, making this also the most studied dose in the literature. Eight of these compared it to a placebo and one study compared it to 100 mg of tramadol. Starting with the studies that compared dexamethasone with a placebo.

Nortcliff et al[21] had a large risk of bias in that the results of 9% of the randomized patients were not analyzed, for various reasons. Additionally, they did not perform an intention-to-treat analysis. Selzer et al[22] also had a high risk of bias because the results of 10% of the randomized patients were not analyzed. They did perform an all-subjects-as-treated analysis but this is discouraged in Cochrane's handbook of ROB2 analysis.

Mehdiratta et al[19] were the only ones who looked at the three outcome parameters. However, they could not demonstrate a significant difference in any of the three (Numeric Rating Scale (NRS), total consumption of analgesic and time to first analgesic request). They used dexamethasone with a multimodal pain regimen.

Ituk et al[18] also could not find a significant difference in pain score (NRS) and total opioid consumption when 8 mg of dexamethasone was added to a multimodal pain regimen. Importantly,

the pain scores in both groups were already very low (<2).

Jafaarpour et al[15] could demonstrate a significant difference in pain score and diclofenac and pethidine consumption. However, the clinical relevance of the decrease in pain score can be questioned as it was already very low in both groups (maximum 3.5 in the plaecbo group). Shalu et al[16] also demonstrated significantly lower pain scores but with a questionable clinically significant effect with a maximum mean difference of 1.5 and minimum 0. They also found a longer time to first analgesic need in the group receiving IV 8 mg dexamethasone.

The next study that compared 8mg of dexamethasone with a placebo was this one by Sharaki et al[14]. They had a significant decrease in pain scores with a maximum mean difference of 5.1 (after 15 min) and a minimum mean difference of 1.3 (after 24h), this seems to have greater clinical relevance than the previous studies. In addition, they were also able to demonstrate a significantly lower morphine consumption (from 8mg to 4mg). In this study, a postoperative multimodal pain management was not applied.

Wu et al[17] studied IV 8 mg dexamethasone in the context of PONV but also reported pain scores. They found significantly lower pain scores when comparing 8 mg with placebo, when comparing 4 mg with placebo, and when comparing 8 mg with 4 mg. However, the clinical relevance of this is very limited considering the mean pain scores were already very low (maximum mean pain score 1.7).

Edomwonyi et al[20] compared IV 8 mg dexamethasone with tramadol. They looked at the three outcome parameters. They could only show a significant difference in pain score at 30min and 1h postoperatively and this in favor of tramadol. But again, the clinical relevance of this is very limited because the mean pain scores were already low (≤2.9). In addition, there was also a significantly lower pethidine consumption in favor of tramadol.

A higher dose of 10 mg dexamethasone was studied by Cardoso et al[23] with a significantly lower number of patients with pain compared to placebo, but they did not study pain scores. Also this was the only outcome parameter they analyzed. Therefore, this is not a good study to draw a conclusion about the results.

Based on the literature found, there might be a tendency towards a limited analgesic effect of 8 mg of dexamethasone. However, in order to make a proper decision here, a meta-analysis may bring more clarity.

Three articles studied the PN use of dexamethasone, adding 4 mg, 5 mg and 8 mg at the TAP block and comparing it to a placebo.

The risk of bias analysis for Gupta et al[24] showed a high risk because this was a single-blind study and because poor data for opioid consumption and time to first analgesic need were analyzed from 27 of the 45 randomized patients.

Liu et al[25] showed a significant decrease in pain score but it is important to mention that the pain scores in the group with only a TAP-block were already low (maximal mean VAS 3.625), so the clinical relevance is difficult to estimate. Besides the limited effect on the pain score, there was a significant decrease in the number of presses on PCIA (mean difference of 2.75).

The only study that looked at the three outcome parameters in PN use was this one by Akkaya et al[26]. Here, in the group of TAP block with placebo, a low pain score was already present (maximum ≤3). The decrease in pain score was further supported by a significant reduction in total tramadol consumption (mean difference of 42.9) and a longer time to first analgesic need.

Judging from the last two studies, there possebly seems to be a limited effect with the PN use of dexamethasone. However to draw firm conclusions a meta-analysis should be done.

The last study, by Maged el al[27], compared SC 16 mg dexamethasone with IV 16 mg dexamethasone and with a placebo. They looked at pain scores and analgesic consumption. The pain scores were statistically significant and the mean difference in pain scores in the IV group vs placebo (max 2.83; min 0.75) and in the SC group (Max 4.75; min 2) also suggest a clinically relevant effect. Between the IV and SC group, there was no significant effet. To analyze analgesic consumption, they looked at the number of patients who required additional morphine and not the total dose consumed. This analysis might be less appropriate because changes in total morphine consumption will be picked up more quickly if one wants to study the (limited) effect of a co-analgesic.

Gynecologic laparoscopy

The 2019 PROSPECT guidelines give dexamethasone a place as an anti-emetic and co-analgesic in a multimodal pain regimen in laparoscopic hysterectomy, but no dose was recommended. Here we give an overview of the literature of how and at what doses dexamethasone has been studied, not only in laparoscopic hysterectomy but more general in gynecologic laparoscopy. Important to note is that also here there was a difference in timing of administration and use of a postoperative multimodal pain regimen.

The IV use of 8 mg dexamethasone was the most studied with six studies in total. Of these, five

studies focused on the use in PONV and reported one or more outcome parameters related to pain (pain scores, total postoperative analgesic use and time to first analgesic need). None of these five studies could demonstrate a significant difference on any of the three outcome parameters.

Only one study, this one by Thangaswamy et al[29], studied IV 8mg dexamethasone versus placebo. They were also the only ones to look at the three outcome parameters but not within a mulimodal postoperative pain management. Interestingly, here the mean VAS scores were already low in all groups ($\leq$35mm on a 100mm scale), they could not demonstrate a significant difference between 4 mg dexamethasone and the placebo group, nor between 8 mg dexamethasone and the placebo goup. Total postoperative fentanyl consumption was significantly lower (mean difference 99.7 µg (in 8 mg vs placebo) and 108.5 µg (in 4 mg vs placebo) and time to first analgesic requirement was also significantly longer.

Two articles studied 5 mg dexamethasone. Chu et al32 studied this in the context of PONV but they also looked at pain scores and analgesic consumption. There was no significant difference on either outcome parameter. It should be noted that they did not look at the consumed dose of analgesic (ketorolac/meperidine) but at the number of patients that needed extra analgesia. In addition, the mean VAS was already low(between 2 and 4) in all groups throughout the postoperative period. According to the risk of bias analysis, the study by Jokela et al[30] had a high risk of bias because no "intention-to-treat analyse" was performed and 8% of patients randomized were not included in the analysis. Thus, the results of this study should be viewed with caution. They could only observe a significantly lower oxycodone consumption in the 10 mg dexamethasone group versus placebo and in the 15 mg dexamethasone versus placebo group.

Corcoran et al[31] studied the effect of 4 mg dexamethasone on the immune system in gynecological laparoscopy, in addition they reported pain scores. However, given that ten of the thirty-two patients dropped out after randomization, there is a high risk of bias with this study.

Kassim et al[28] were the only ones to study the dose dependent on the weight (0.1 mg/kg). This was a good quality study that also studied the three outcome parameters but none of them showed a significant difference when dexamethasone 0.1mg/kg was added to duloxetine. It is noteworthy that there were already low pain scores (<4) in the early postoperative period (2 to 6h).

The studies examining 4 mg and 5 mg IV dexamethasone are of questionable design and thus no conclusions can be drawn here. The only study that had IV 8 mg dexamethasone as its primary endpoint does show a positive effect on fentanyl consumption and longer time to first analgesic requirement but not on pain score. With this one study, no conclusions can be drawn about an analgesic dose of dexamethasone in a multimodal pain management.

Two studies studied the IP use of dexamethasone, both using 16 mg dexamethasone. Nouri et al[38] had a high risk of bias because their randomization was not random, as they stated in their article. In addition, there was no clarity on whether the data of all patients were analyzed after radomization.

Asgari et al[39] did not report exact pain scores but they stated that "Patients' pain severity increased in the placebo group and after 8 hours it started to decrease; whereas, in the dexamethasone group, the average pain severity was less than 3 (P<0.001)." The mean pethidine consumption was significantly lower, though rather limited (mean difference 8.4).

An unequivocal conclusion about the IP use of dexamethasone cannot be made based on this literature.

One study, by Ismail et al[40], compared IP and IV use of 8 mg dexamethasone. They could not demonstrate a significant difference in pain score but importantly, in both groups the mean VAS was already very low (<3.1). The second and final outcome parameter, namely total pethidine use, was also not significantly different. So the IV or IP use of dexamethasone does not seem to make a difference here.

Oncologic breast surgery

For oncological breast surgery, PROSPECT guidelines were published in 2020[55]. These recommend dexamethasone for prevention of PONV and as an analgesic in a multimodal pain regimen. Also here no dosage was mentioned. We wanted to know how and at what dosage dexamethasone is used as an analgesic.

In this type of surgery, with three studies, IV use 8 mg dexamethasone versus placebo was the most studied. There are a few things that stand out about these studies.

Only Bakeer et al[45] studied the effect of 8 mg dexamethasone most extensively on the three outcome parameters (pain score, analgesic consumption and time to first analgesic need). They found a significant improvement in all these outcome parameters, with a maximum median difference in VAS of 4 and a minimum median difference of 2. It shows that dexamethasone prolongs the duration of PVB. Gomez-Hernandez et al[41] and Cortés-Flores et al[42] studied only pain scores

and analgesic requirement. Interestingly, Cortés-flores et al already had low pain scores (VAS<4) in the placebo group. The differences in pain scores between the two groups were statistically significant but very small. This study also studied the number of patients needing additional morphine and not the difference in total morphine dose between the two groups. None of the three studies had a postoperative multimodal pain management.

Steinthorsdottir et al[43] studied the highest IV dose of dexamethasone (24 mg) and compared this to IV 8 mg. This could be an interesting study to see if there is a dose dependent effect of dexamethasone but this however is not the design of the study. Pain was a secondary endpoint, they only looked at pain scores as an outcome parameter and no comparison was made with a placebo group.

Hval et al[44] compared only two of the three outcome parameters (pain scores and analgesic consumption). In the placebo group, they already had a low median VAS (≤2) at all time points.

We cannot draw conclusions on the IV dose used as co-analgesic in oncological breast surgery with the literature found.

The PN use of dexamethasone was studied by El Mourad et al[46] and Kumar et al[47].

Neither study used a multi-modal pain management postoperatively. El Mourad et al[46] were the only ones who self-reported finding a statistically significant decrease in pain score but with clinically limited significance. They had a significantly lower postoperative morphine use and longer time to first analgesic need.

In the study by Kumar et al[47] the maximum mean difference was 1.1 with in the placebo group a maximum mean VAS of 2.8±1.3. This is statistically significant but again one can question whether this is clinically significant. In addition, there was a median difference of only 10min between the two groups for time to first analgesic need.

These studies (Bakeer et al[45], El Mourad et al[46] and Kumar et al[47]) suggest that dexamethasone PN or IV significantly prolong the duration of nerve block but in the case of the study by Kumar et al, questions can be raised about its clinical relevance.

Side effects of intravenous use of dexamethasone

Side effects of corticoids that may have important consequences in the post-operative period are hyperglycemia, problems with wound healing and risk of wound infections due to their immunomodulatory effect. A number of recent reviews have looked at this in more detail. In the 2017 DREAMS trial, there was no higher risk of wound healing problems with 8 mg IV dexamethasone. A 2019 systematic review with 37 trials and more than

4,000 patients also showed no higher risk of wound healing problems within 30 days after surgery at doses up to 20 mg of dexamethasone. Higher doses were not included in this review. The PADDI trial from 2021 showed in a study population of 8725 patients undergoing non-cardiac surgery of at least 2 hours with an incision > 5 cm, no increased risk of wound infections with a single dose of 8 mg dexamethasone within 30 days after surgery. As expected, there was an increase in blood glucose of 0.7 mmol/L (12.6 mg/dl) in patients without diabetes. This increase is limited and not clinically relevant in this population[57]. Hyperglycemia is more pronounced in patients with diabetes mellitus. In the subgroup with pre-existing diabetes mellitus in the PADDI trial, the median increase in blood glucose was 1.3 mmol/L (23.4 mg/dl)[58]. The clinical relevance is that glucose levels need to be monitored more frequently and there may be a temporary need for more insulin. In view of the reassuring results of the above-mentioned studies, a single IV dose of dexamethasone up to 20 mg seems safe. For IV use in elective cesarean section, however, one should consider the timing of administration. If it is given before clamping the umbilical cord, it is possible that dexamethasone may enter the fetus's circulation. The effects of dexamethasone on the fetus have not yet been investigated.

Limitations

We did not conduct a systematic review or meta-analysis of the data, so we cannot give any conclusions about the most appropriate dose of dexamethasone in whatever route of administration (IV, IP, PN or SC).

We did not study the intrathecal use of dexamethasone. The studies we found showed a great variation in study protocol and studied outcome. Also based on the ROB2 assessment tool of COCHRANE, some studies had a great risk of bias. We only searched for dexamethasone and not for other corticoids as co-analgesic.

Conclusion

This literature review provides an overview of the use of dexamethasone in elective cesarean section, laparoscopic surgery and oncological breast surgery. Three routes of administration were examined: intravenous, perineural and intraperitoneal.

The most commonly studied intravenous dose was 8 mg of dexamethasone in the three types of surgery, with a dose ranging from 4 mg to 24 mg. In elective cesarean section there might be a tendency towards a limited analgesic effect of 8 mg of dexamethasone.

In perineural use the dosage ranged between 4 mg and 8 mg. And for intraperitoneal use the only dosage that was studied was 16 mg.

Because of the great variation of study protocols and outcomes we cannot draw any conclusions regarding the analgesic dosage of dexamethasone based on this literature study. A systematic review and meta-analysis may help to address this question.

For future RCT's we advise to prioritize pain scores, total analgesic dose consumption and time to first analgesic requirement as the primary endpoint. It is also important to implement a multimodal pain regimen as this should be part of standard postoperative care.

Conflict of interest: The authors report no conflicts of interest in this work.

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