

Review

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Role of Dexamethasone in Peri-operative Anesthesia Management: A Review of Literature

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ABSTRACT

Dexamethasone has been used widely in clinical specialties including anesthesia. It is regarded as one of the ideal peri-operative agent being readily available, cheap, anti-inflammatory agent, prevents and treats post-operative nausea and vomiting (PONV), promotes appetite, suppress inflammation, a good analgesic agent both as intravenously or as an adjuvant to peripheral nerve blocks, it provides a sense of well-being and is considered to have a good quality of recovery and early discharge in patients from anesthesia. Controversial role of dexamethasone in causing post-operative surgical site infections have been solved and overall adverse effects of dexamethasone are rare and its benefits out-weighs the risks involved. The author did a literature search in Google Scholar and PubMed databases (latest articles related to the role of dexamethasone in peri-operative period over a period of two years 2015-17).

KEY WORDS: Dexamethasone; Peri-operative agent; Anesthesia.

KEY MESSAGES: Dexamethasone has a tremendous role in preventing post-operative nausea and vomiting, it has a fair analgesic action if given intravenously, epidurally or perineurally, patients receiving dexamethasone have enhanced recovery profiles after surgery and single dose would usually not increase the risk of surgical site infections. Overall adverse effects of dexamethasone are rare and its benefits out-weighs the risks involved.

ABBREVIATIONS: COPD: Chronic Obstructive Pulmonary Disease; PONV: Post-operative Nausea and Vomiting; TIVA: Titrated Total Intravenous Anesthesia; AVN: Avascular Necrosis; POCD: Post-operative Cognitive Decline; TPVB: Thoracic Paravertebral Block; PACU: Post Anesthesia Care Unit; GABA: γ -aminobutyric acid; DNB: Dental Nerve Block; TMS: Third Molar Surgery.

INTRODUCTION

Glucocorticoids have been used to reduce inflammation and tissue damage in a variety of conditions, including inflammatory bowel disease, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease (COPD), acute laryngotracheobronchitis, cerebral edema, severe allergy or anaphylaxis, promote lung maturation in pre-term and some malignancies to counteract inflammatory and nausea vomiting side effects of chemotherapeutic agents. Dexamethasone is a synthetic glucocorticoid which has minimal mineralocorticoid activity. It is a potent anti-inflammatory drug with thirty to forty times the potency of hydrocortisone and is up to sixteen times as potent as prednisolone.

AN IDEAL PERI-OPERATIVE AGENT AND MECHANISM OF ACTION

Dexamethasone has been used widely in clinical specialties including anesthesia. The biological half-life is about 3 hours, although the duration of action may be much longer. Dexamethasone is bound to plasma proteins in much lower-levels than other glucocorticoids. Hepatic metabolism (both glucuronidation and sulfation) occurs to produce inactive metabolites, with

65% of the dose of dexamethasone excreted in the urine within 24 hours, with less than 3% unchanged.

It is regarded as one of the ideal peri-operative agent being readily available, cheap, anti-inflammatory agent, prevents and treats post-operative nausea and vomiting (PONV), promotes appetite, suppress inflammation, a good analgesic agent both as intravenously or as an adjuvant to peripheral nerve blocks, it provides a sense of well-being and is considered to have a good quality of recovery and early discharge in patients from anesthesia. It has a complex mechanism of action involving binding of steroid ring to the receptor effect site, which results in gene transcription, and resulting in decreased release of mediators like bradykinin, IL 1, 2 and 6, resulting in pain relief.

DEXAMETHASONE: ROLE IN PONV

The mechanism of action of dexamethasone as an antiemetic agent, is unknown, there are various postulated mechanism is depletion of γ -aminobutyric acid (GABA) stores, and reduction of blood brain barrier to emetogenic toxins, inhibition of central prostaglandins and serotonin. There are tremendous literature available which suggest that dexamethasone reduce the incidence of post-operative nausea and vomiting. In one of the biggest DREAMS trial collaborators, 1350 participants were randomly allocated to dexamethasone and control group, and it was found that a single dose of 8 mg dexamethasone reduced the incidence of nausea and vomiting till 24 hours and rescue anti-emetics were not required till 72 hours in patients who underwent bowel surgeries with no adverse events.¹

Vlok found that there is a significant reduction in post-operative nausea and vomiting and post-operative pain as compared to tramadol, pethidine, magnesium sulphate and tramadol.² Sehavat et al suggested that a single prophylactic dose of dexamethasone 8 mg after an operation can reduce post-operative nausea and vomiting.³ Naryanappa et al suggested that combination of dexamethasone and ramosetron is more effective than palonosetron in PONV prevention, and they did their study in gynecological surgeries under spinal anesthesia.⁴

While there were researchers who were publishing astonishing results of dexamethasone as a good prophylactic and therapeutic agent for PONV, there were concerns which were raised suggesting the risk of surgical site infections. Kurz et al did investigations and found that a single dose of dexamethasone used in peri-operative period does not increase the risk of surgical site infections.⁵ However, the combination of dexamethasone and ondansetron was not effective in preventing PONV or severe PONV in obese patients undergoing laparoscopic sleeve gastrectomy after titrated total intravenous anesthesia (TIVA).⁶

DEXAMETHASONE: ANTI-INFLAMMATORY ACTION

Research on clinically significant anti-inflammatory action of dexamethasone has been studied in dental, ear nose and throat

(ENT) surgeries. Dexamethasone in dosage of 0.5 mg/kg reduces edema and also has been found to modulate bronchial hyper reactivity in asthmatic patients. Yang et al have found that a single bolus of 10 mg dexamethasone at the time of induction in thyroidectomies reduced the incidence as well as severity of post-operative sore throat during swallowing at 24 hours after surgery.⁷ However, Kamranmanesh et al studied the role of dexamethasone in pediatric age group and found that the incidence of cough (31% vs. 34%), laryngospasm (16% vs. 14%), apnea (9% vs. 5%), desaturation (4% vs. 5%), bronchospasm (14% vs. 7%), vomiting (4% vs. 6%), and post-operative symptoms (8% vs. 7%), were less but not significantly different in patients receiving dexamethasone and placebo group.⁸ Lim et al in their prospective randomized double-blind study suggested that a single pre-operative dose of dexamethasone *versus* methylprednisolone was equally effective in reducing post-operative swelling and trismus.⁹

EFFECT ON NEUROMUSCULAR BLOCKADE

So et al have found that a single dose of dexamethasone in dosage of 8 mg administered 2-3 hours prior to surgery have shortened the onset and recovery times of cis-atracurium induced block by 15% by enrolling one hundred seventy patients into 3 groups, and patients received 8 mg dexamethasone. Three minutes after anesthesia induction, intubation was performed without neuromuscular blockers, and acceleromyography was initiated. All patients received 0.05 mg/kg cisatracurium; the onset time and recovery profiles were recorded. The recovery time [mean (95% CI) minutes] was significantly hastened in dexamethasone group [28.5 (27.3-29.6)] compared to that in control group [32.3 (31.0-33.6)] ($p < 0.001$) and control group [30.9 (29.9-31.8)] ($p = 0.015$). The total recovery time was significantly hastened more in dexamethasone group [47.1 (45.5-48.6)] than group control [52.8 (51.6-54.0) minutes] ($p < 0.001$) and control group [50.5 (48.7-52.3) minutes] ($p = 0.008$).¹⁰

ANALGESIC EFFECT OF INTRAVENOUS DEXAMETHASONE

Analgesic action of dexamethasone has been found in dental surgeries (e.g., tooth extraction), ENT surgeries (e.g., mastoidectomy, tonsillectomy, adenoidectomy, etc.), ano-rectal surgeries. Even its role has been well defined in total knee arthroplasty, Samona et al have used a single dose of dexamethasone and have found that there is significant reduction in narcotic consumption and significant decrease in pain scores at 24 hrs. It also appears to be a safe modality in patients undergoing total knee arthroplasty (TKA) with no increase in wound related complications.¹¹ Jain et al have compared different dosage of dexamethasone and have found that 16 mg reduces post-operative pain on motion at 24 and 36 hours.¹² Role of intravenous dexamethasone has not just confined to systemic analgesia rather its role has been defined in prolonging the peripheral nerve blockade. Addition of dexamethasone both intravenously and caudally as an adjuvant to caudal ropivacaine has been found to reduce the intensity of post-operative pain and prolonging the post-operative analge-

sia.¹³ Chalifoux have found that low doses of intravenous dexamethasone (4 mg and 10 mg) significantly prolongs the analgesic duration of interscalene block.¹⁴

The mean visual analog scale (VAS) was significantly lower in the Group C for up to 24 h following the caudal block. No significant hemodynamic changes were noted in any of the groups. The intravenous dexamethasone group showed higher blood glucose levels at 24 h but was not clinically relevant. These results suggest that injection dexamethasone is a safe adjunct to caudal ropivacaine in lumbosacral spine surgeries.¹⁵ The authors concluded that administration of dexamethasone 8 mg intravenously prolongs the duration of post-operative analgesia and sensory block in patients undergoing lower segment cesarean section under spinal anesthesia.¹⁶

ROLE OF EPIDURAL DEXAMETHASONE IN CENTRAL NEURAXIAL BLOCKADE

The mechanism of action by which epidural or perineural dexamethasone acts is unknown, some believe it to be because of direct membrane stabilizing effect on nerves or direct action on spinal cord by means of transcription factors like nuclear factor kappa B (NF- κ B). Hong et al have used epidural dexamethasone and found that 10 mg epidural dexamethasone was more effective than lower dosage in patients undergoing gastrostomy, associated with moderate to severe intensity of pain. Total fentanyl consumption was also significantly less in dexamethasone group and no difference in adverse events like hypotension, bradycardia, post-operative nausea and vomiting and urinary retention were found.¹⁷

PERINEURAL DEXAMETHASONE

Dexamethasone prolongs the action of lignocaine 2% in dental nerve block (DNB) for third molar surgery (TMS). Study found maximum duration of DNB in study group (SG) was 248.88 min and in control group (CG) was 175.44 min.¹⁸ In a study by Zhao et al it was found that perineural dexamethasone prolongs the analgesic duration as compared to intravenous route only when epinephrine is coadministered. Without epinephrine, the two modalities show equivalent effect as adjuvants on regional anesthesia.¹⁹ Razavizadeh et al affirmed that adding dexamethasone to bupivacaine in patients undergoing herniorrhaphy in inguinal area significantly prolongs the duration of post-operative analgesia.²⁰ Ribeiro et al have found a significant increase in duration of analgesia in dexamethasone group in 0.1 mg/kg dosage as compared to placebo with bupivacaine in upper limb surgeries in pediatric age group. The duration of analgesia in the group BD was 27.1 \pm 13.4 hours and was significantly higher as compared to the group B, in which it was 13.9 \pm 11.3 hours (p <0.05) receiving dexamethasone (0.1 mg/kg) as an adjunct to bupivacaine 0.125%.²¹

Similar result has been shown by Akram et al in finding improved tolerance in hand and forearm surgeries and bet-

ter analgesia in group receiving dexamethasone as compared to lignocaine and ketorolac, and the difference being statistically significant.²²

Addition of dexamethasone to ropivacaine in transversus abdominis plane (TAP) blockade has also been found to have prolonged analgesia and reduced analgesic requirement in total abdominal hysterectomy. Post-operative VAS pain scores were significantly lower at 4, 6, and 12 h in Group Ropivacaine Dexamethasone (RD) as compared to Group Ropivacaine (R) alone (p <0.05). Significantly longer analgesia (13.2 \pm 7.6 vs. 7.1 \pm 4.6 h, p <0.001) with lesser tramadol requirement in first 24 h (50.2 \pm 34 vs. 94 \pm 35 mg, p <0.001) were observed in Group RD as compared to Group R.²³

Dexamethasone 300 μ g/kg with ropivacaine intra-articular has a superior analgesic efficacy a much prolonged post-operative pain relief, minimal post-operative analgesia requirement and better patient compliance with negligible side effects. Liu et al did a prospective observational study and used a single shot of bilateral thoracic paravertebral block (TPVB) with 25 ml of 0.2% ropivacaine and 5 mg dexamethasone in combination for both sides at the 8th thoracic transverse level (T8) performed on 201 participants who complained moderate to severe pain on arrival to postanesthesia care unit (PACU) after laparotomy. The VAS pain scores at rest and on cough were 7.9 \pm 1.6 and 8.7 \pm 1.3 respectively pre-bilateral TPVB. The VAS pain scores at rest and on cough were significantly decreased to 1.1 \pm 1.2 and 2.1 \pm 1.6 respectively (p <0.001) at 60 min after bilateral TPVB and to 2.1 \pm 1.7 and 3.8 \pm 1.9 at rest and on cough respectively (p <0.001) at 24 h after bilateral TPVB. At 10 min post-bilateral TPVB, only systolic blood pressure was reduced from 122 \pm 19 mmHg to 111 \pm 18 mmHg (p =0.007) but then gradually became stable.²⁴ In addition to its useful effects, dexamethasone has been tried in combination to ropivacaine in ankle block and the combination has been found to improve pre-emptive ankle block by decreasing post-operative pain intensity and analgesic consumption with minimal post-operative complication.²⁵ However, low dose dexamethasone 2 mg has been found to have only modest and inconsistent effect of questionable clinical relevance on block duration.²⁶

A concern has been raised in a meta-analysis carried out by Chong et al and it was suggested that perineural dexamethasone prolongs the duration of analgesia and the magnitude of effect of 3.77 hours (95% confidence interval [CI], 1.87-5.68 hours; p <0.001) compared to IV dexamethasone, with high statistical heterogeneity) raises the question as to whether perineural dexamethasone should be administered routinely over its IV counterpart or reserved for selected patients where such prolongation would be clinically important. For secondary outcomes, perineural dexamethasone prolonged the duration of both motor (3.47 hours [95% CI, 1.49-5.45]; p <0.001) and sensory (2.28 hours [95% CI, 0.38-4.17]; p =0.019) block compared to IV administration. Furthermore, perineural dexamethasone patients consumed slightly less oral opioids

at 24 hours than IV dexamethasone patients.²⁷

ROLE OF DEXAMETHASONE IN SHIVERING

Moeen et al have shown in their study done during transurethral prostatectomy that intrathecal dexamethasone was as effective as intrathecal meperidine in attenuation of shivering compared to placebo under spinal anesthesia with less adverse events. The number of patients with shivering was higher in Group Control (C) (13) than in Group Dexamethasone (D) (2) and Group Meperidine (M) (3) with no differences between Group D and M; $p=0.001$. Intensity and recurrence of shivering and dose of IV meperidine used to treat shivering were higher in Group C compared to Group D and Group M; $p=0.01$, $p=0.064$, and $p=0.004$, respectively.²⁸

MISCELLANEOUS ROLE OF DEXAMETHASONE

Karman et al suggested that the co-administration of dexamethasone and sevoflurane may ameliorate short-term and long-term cognitive dysfunctions induced by sevoflurane in adult rats. Sevoflurane may impair spatial learning and short-term and long-term memories in adult rats.²⁹

In severe to profound sudden deafness refractory to conventional ST, the daily perfusion of 4 mg/ml DEX through an intratympanic catheter is an easy, well accepted procedure that enables patients to receive a drug in the middle ear in a repeatable or sustained form, with minimal discomfort and a partial rescue (67.86%) and a speech recognition gain of 39% as suggested by Zanetti et al.³⁰

CONTROVERSIAL ROLE IN WOUND INFECTION

In the largest ENIGMA II TRIAL, there were registered 5499 subjects, and it was found that dexamethasone administration was associated with a decrease in fever on days 1-3 [182 (8.4%) vs. 488 (14.7%); RR 0.61; 95% CI 0.5-0.74; $p<0.001$] and shorter lengths of stay in hospital [propensity score-adjusted median (IQR) 5.0 (2.9, 8.2) vs. 5.3 (3.1, 9.1), $p<0.001$]. Neither diabetes mellitus nor surgical wound contamination status altered these outcomes. Dexamethasone was administered to 2178 (40%) of the 5499 subjects included in this analysis and was not associated with wound infection [189 (8.7%) vs. 275 (8.3%); propensity score-adjusted relative risk (RR) 1.10; 95% confidence interval (CI) 0.89-1.34; $p=0.38$], severe post-operative nausea and vomiting on day 1 [242 (7.3%) vs. 189 (8.7%); propensity score-adjusted RR 1.06; 95% CI 0.86-1.30; $p=0.59$], quality of recovery score [median 14, interquartile range (IQR) 12-15, vs. median 14, IQR 12-16, $p=0.10$], length of stay in the post-anesthesia care unit [propensity score-adjusted median (IQR) 2.0 (1.3, 2.9) vs. 1.9 (1.3, 3.1), $p=0.60$], or the primary outcome of the main trial.³¹ And it was concluded that dexamethasone administration to high-risk non-cardiac surgical patients did not increase the risk of post-operative wound infection or other adverse events up to day 30, and appears to be safe in patients either with or

without diabetes mellitus. Also in retrospective analysis done by Richardson et al, a single intravenous peri-operative dose of dexamethasone had no statistically significant difference in the rate of post-operative joint infections after total hip or knee arthroplasty.³²

QUALITY OF RECOVERY

Mihara et al have determined the quality of recovery using QoR-40 questionnaire and indicated that peri-operative dexamethasone administration may improve short-term (i.e., one day) quality of recovery after general anesthesia and surgery.³³ In another randomized control trial done by Sakamoto et al, have demonstrated a better quality of recovery in patients' receiving dexamethasone compared to control for a bilateral inguinal hernia repair surgery.³⁴ Use of dexamethasone prior to vaginal reconstructive surgery was associated with less nausea/vomiting and need for antiemetics as well as greater success with voiding trials. Furthermore, quality of recovery was enhanced, suggesting use of dexamethasone should be considered for these patients as suggested by Pauls et al³⁵ Valentin et al, have revealed that dexamethasone can reduce the incidence of post-operative cognitive decline (POCD) in elderly patients undergoing surgery, especially when associated with BIS 46-55. The effect of dexamethasone on S100 β might be related with some degree of neuroprotection. Neuropsychological tests showed that dexamethasone associated to BIS 46-55 decreased the incidence of POCD, especially memory and executive function. The administration of dexamethasone might have prevented the post-operative increase in S100 β serum levels.³⁶

ADVERSE EFFECTS OF DEXAMETHASONE

There are few authors who suggest that peri-operative administration of dexamethasone during neurosurgical procedures can cause significant increase in blood glucose concentration especially in patients who receive dexamethasone intra-operatively.³⁷

Dexamethasone is particularly contraindicated in systemic fungal infections and before the administration of live or attenuated vaccines because the response to these vaccines cannot be predicted. The use of dexamethasone in oral cancer patients with microvascular reconstruction did not provide a benefit. More major complications, especially infections, occurred in patients receiving dexamethasone. Their data thus did not support the use of peri- and post-operative dexamethasone in oropharyngeal cancer patients undergoing microvascular reconstruction.³⁸

Dexamethasone 8-10 mg is associated with a significantly greater peri-operative increase in blood glucose compared with a 4 mg dose. This model estimated the increase in post-operative glucose to be 25 mg/dL higher over 24 hours with dexamethasone 8-10 mg than with 4 mg (95% confidence limits, 18-32 mg/dL).³⁹

Avascular necrosis (AVN) of both the humeral and femoral heads is a known complication of chronic steroid use; however, single dose of dexamethasone usually won't cause AVN. Dexamethasone induced pruritus is a known entity, and usually patients experience genital or anorectal or perineal pruritus. It is usually short lived lasting 2-45 seconds and phosphate group is the postulating factor for the same. It is more commonly seen in females and is avoided by either giving dexamethasone slow or by addition of lidocaine.⁴⁰

LIMITATION OF THE STUDY

This is not a systematic review and remains author's interpretation.

CONCLUSION

Considering the benefits of dexamethasone, there is increasing trend towards its use. Not just it is helpful in preventing postoperative nausea and vomiting, also it has a good analgesic action both intravenously, epidurally or perineurally. Patients have enhanced recovery profiles after surgery and single dose would usually not increase the risk of surgical site infections. It has an enhanced anti-inflammatory action and is a preferred drug during inflammatory situations like asthma, chronic obstructive pulmonary disease (COPD), laryngotracheal bronchitis and laryngospasm. Controversial role of dexamethasone in causing post-operative surgical site infections have been solved and overall adverse effects of dexamethasone are rare and its benefits out-weighs the risks involved.

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