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NEW STUDIES ON DEXKETOPROFEN

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ABSTRACT

Introduction. Dexketoprofen(DEX) belongs to nonsteroidal anti-inflammatory drugs (NSAIDs) and has analgesic, anti-inflammatory, and antipyretic properties. DEX is an enantiomer of ketoprofen (S+) and has a stronger effect than ketoprofen. It is highly effective even after the administration of small doses. The therapy with DEX does not cause serious side effects and is additionally tolerated by the body.
Aim. The review aimed to find original scientific publications on DEX in recent years and its therapeutic efficacy, safety, and tolerability.
Method. A systematic review of scientific articles published no earlier than 2015 was carried out. Materials from the PubMed, Google Scholar, and Medline Complete databases were used. The literature review was carried out in November 2021. Among the publications found, 28 scientific articles were selected for analysis.
Results and discussion. Over the recent years, there have been many publications about DEX. Articles describing new data on DEX in the treatment of pain were analyzed, compared with other drugs and mesotherapy, the latest reports of its combination with tramadol and thiocolchicoside were reviewed, and a new slow release form of DEX and new therapeutic applications of this drug were investigated. After analyzing all the studies, it was found that DEX produced similar or more effective analgesia compared to other drugs and reduced the need for emergency medications. In addition, it was noted that using DEX in combination therapy was far better than taking it alone, and was also found to be effective in raising the epileptic threshold. Mesotherapy achieved higher results in the treatment of pain symptoms compared to DEX. The side effects that appeared as a result of the use of DEX therapy were not life-threatening.
Conclusion. The results of the review confirm that DEX is a very good analgesic, which is more potent than paracetamol and diclofenac sodium while having similar effects to dexmedetomidine and lidocaine. DEX in combination with tramadol or thiocolchicoside is more effective than when the two drugs are used alone. Scientists are working on the long-acting DEX and are looking for new applications of the drug in epilepsy and oncology.
Keywords: dexketoprofen, pain, tramadol, nonsteroidal anti-inflammatory drugs.

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INTRODUCTION

DEX belongs to a non-steroidal anti-inflammatory drugs (NSAIDs). DEX is a propionic acid derivative - (S+) enantiomer of K with analgesic, anti-inflammatory and antipyretic properties. The action of the drug is mainly based on the inhibition of cyclooxygenases (COX) [1]. The use of a single isomer of K simplifies the pharmacokinetics of the drug and allows a reduction of 50% in its effective dose, reducing the number of serious side effects [2,3].

The analgesic effect of DEX lasts for 4-6 h and begins approximately 30 min after administration. The half-life (T1/2) in the elimination phase is 1.65 h. Tmax - 30 min. After conjugation with glucuronic acid in the liver, DEX is mainly excreted by the kidneys. Only the S (+) enantiomer is detectable in the urine. The drug does not accumulate in the body [1,4].

DEX is available in Poland in the form of tablets and granules for oral solution and in injection solution. DEX is very effective in treating nociceptive, somatic, visceral and inflammatory pain. It is used for the symptomatic treatment of mild to moderate chronic pain and in the treatment of moderate to severe acute pain [1].

The side effects of DEX may be in the following areas: the gastrointestinal tract, the circulatory system, respiratory system, the central nervous system, liver, kidneys, ear and labyrinth, systemic reactions, deterioration of the number and function of platelets, photosensitizing effect on the skin [5]. In 2015 Olmez et al. described esophagitis due to DEX [6]. DEX may have cytostatic, cytotoxic and genotoxic effects on healthy human lymphocytes, depending on the concentration and duration of exposure [7]. Kayipmaz et al. described acute dystonic reaction [8].

In this study authors try to describe the latest information about DEX based on medical literature from 2015.

MATERIALS AND METHODS

Standard up-to-date criteria were followed for review of the literature data. A search for English-language articles in the PubMed, Medline Complete, Google Scholar database was performed. The databases were searched in November 2021 with phrases: 'dexketoprofen', 'dexketoprofen and treatment', 'dexketoprofen and tramadol'. More than 700 results were found. A total of 388 articles published between 2015 and November 2021 were scanned. After skimming abstracts, 28 articles were chosen for this systematic review

RESULTS AND DISCUSSION

Piirainen A. et al. conducted a double-blind, randomized clinical trial to determine the effective dose of DEX for pain relief as well as its effect on the economy of oxycodone in patients undergoing laparoscopic cholecystectomy (LCC) [9]. The study involved 22 patients, 18-65 years of age, who underwent LCC and received 0.2 mg/kg of oxycodone during induction of anesthesia.

Then they were randomly divided into two groups. 10 patients received intravenous DEX 10 mg and 12 patients 50 mg. The pain was assessed every 10 minutes using the numerical rating scale (NRS), and then when the resting score was ≥3 / 10 or ≥5 / 10 during compression of the wound, a plasma sample was collected to determine the minimum effective concentration of oxycodone. The results were similar in both groups.

In the 10 mg group of DEX, the median was 60 ng/ml, and in the 50 mg group, the median was 52 ng/ml. Then, depending on body weight and height, patients were administered intravenously 2 or 3 mg of oxycodone every 10 minutes, until the resting NRS was <3/10, and in the case of pressure on the wound <5/10. A second plasma sample was collected to determine the Minimum Effective Analgesic Concentration of oxycodone. For those in the 10 mg DEX group, the median was 98 ng/ml, and for the 50 mg group, the median was 80 ng/ml.

One patient in the 10 mg DEX group and two patients in the 50 mg group experienced only mild pain during the first two hours after surgery and therefore did not receive an opioid. The total amount of oxycodone that was needed to control pain was similar between the two groups. The median for the 10 mg DEX group was 0.11 mg/kg, and for the 50 mg group, it was 0.08 mg/kg. The results of the study show that both 10 mg and 50 mg of DEX have achieved similar analgesic efficacy. The need for acute oxycodone administration was similar in both groups of patients [9].

In 2018 Sánchez-Pérez et al. conducted a double-blind, randomized clinical trial to determine effects of the preoperative administration of DEX on swelling and pain after dental implant surgery [10]. Eighty three patients completed the study. Fifteen minutes before implant surgery patients received an oral dose of 25 mg DEX (41individuals) or placebo -500 mg vitamin C (42 individuals). To evaluate pain a subjective visual analogue scale (VAS) of 100 mm in length was used. Complications and inflammation were assessed using a 5-point Likert scale. During the immediate postoperative period the patients who received DEX reported a lower pain intensity. The inflammatory response was weaker in the DEX group at 48 hours, but bleeding was greater. In conclusion of this study, the preoperative administration of 25 mg DEX orally can reduce the severity of immediate postoperative pain [10].

Demir U. et al. conducted a randomized, double-blind study that evaluated the effect of prophylactic intravenous DEX administration on pain following shoulder arthroscopy [11]. The study involved 60 patients aged 18-65, who were divided into two groups of 30 people each. One group of patients took 100 ml of 0.9% sodium chloride, while the other 50 mg of DEX. In both groups of patients, patient-controlled analgesia (PCA) was used, which was made of 25 μg of fentanyl, and 10 min. locks. Pain measurement was performed with VAS at 15, 30, and 45 minutes and 1, 2, 4, 8, 12, 24, and 48 hours. A higher amount of PCA fentanyl was reported in the control group. There was no significant difference between the two groups in the context of postoperative motor blockade of the shoulder joint, which was assessed by shoulder abduction. A longer duration of pain blockade at the incision site was noted in the DEX group than in the control group. The DEX group had lower VAS scores throughout the study. Nausea and vomiting occurred in 7 patients in the DEX group and 8 in the control group. It was concluded that preventive use of DEX is a good option after shoulder arthroscopy because it is effective in

relieving pain and has no serious side effects or complications [11].

Comparisons with other pain medications Anil A. et al. in a randomized clinical trial compared the effect of a single intravenous administration of DEX and diclofenac sodium (DS) on pain relief in patients after laparoscopic cholecystectomy [12]. Sixty adult patients were divided into two groups. Thirty minutes before the end of the operation, one group of patients received 50 mg of DEX and the other group of 75 mg of DS. In both groups of patients, intravenous patient-controlled analgesia (PCA) was administered, which was performed with a 1 mg/ml dilution of morphine and a 2 mg bolus of morphine. If the pain rating on the VAS was greater than 4, patients were given 20 mg of tenoxicam as a rescue painkiller. In all postoperative periods, patients taking DS consumed more PCA morphine compared to those taking DEX. In the DEX group, the first need for an analgesic in the postoperative period was later than in the DS group. Rescue analgesia use was more often required in the DS group (76%) than in the DEX group (16%). Total morphine consumption was significantly lower in the DEX group (18 mg) as opposed to the DS group (46 mg). The incidence of side effects was low in both groups. In the DEX group, one person developed hypotension, another reported bradycardia, and 3 experienced nausea and vomiting. In the DS group, hypotension occurred in one patient, bradycardia in two, and nausea and vomiting were reported by three patients. The results of the study indicate that taking DEX before the end of surgery provided patients with more effective analgesia compared to patients taking DS [12].

Al. B. et al. compare the analgesic efficacy of DEX, paracetamol, and fentanyl in patients suffering from renal colic in a randomized controlled trial [13]. The study involved 300 patients aged 16-65. Patients were divided into three groups. One group received 50 mg of DEX intravenously, the other group 2 μg/kg of fentanyl, and the last group 10 mg of paracetamol. The pain was assessed using a VAS before drug administration and at 15 and 30 minutes after drug intake. At 30 minutes, DEX was more effective than paracetamol and fentanyl. 57% of patients in the study needed rescue medication. Such drugs could be DEX, paracetamol, fentanyl, tramadol, or DS. The lowest demand for rescue medication was reported in the DEX group (31%), the highest in the paracetamol group (53%). It was concluded that DEX reduces the need for rescue medication and is more effective in reducing pain than fentanyl and paracetamol [13].

Serinken M. et al. in another prospective randomized, double-blind, controlled trial compared the effect of DEX or paracetamol in patients who suffered from primary dysmenorrhea [14]. The study included 99 adult women who received 50 mg of DEX or 1 g of paracetamol intravenously. Pain intensity was measured with a VAS at the beginning and 15 and 30 minutes after drug administration. Both pharmaceuticals showed great efficacy in reducing pain. At the conclusion of this study, it was found that DEX and paracetamol were effective in reducing pain in patients with primary dysmenorrhoea, despite better VAS scores after DEX administration, the difference between the drugs was not statistically significant [14].

Yilmaz A. et al. in a prospective, randomized, double-blind, controlled clinical trial compared the effectiveness of DEX and paracetamol in the treatment of musculoskeletal traumatic pain [15]. The study involved 200 patients aged 24-48. Patients were divided into two groups. One group received 50 mg of DEX and the other group 1000 mg of paracetamol intravenously. The pain was measured using a VAS, a verbal rating scale (VRS), and the NRS before taking the drug and 15, 30, and 60 minutes after administration of the pharmaceutical. After one hour, the study was terminated. During the study, no statistically significant difference in NRS and VAS was found between the paracetamol and the DEX group. According to the VRS, 37 patients in the paracetamol and 57 in the DEX group reported severe pain at the beginning of the study. After 60 minutes, one patient from both groups reported that the severe pain persisted. The study showed that the efficacy of DEX and paracetamol was similar in reducing the intensity of pain in musculoskeletal injury [15].

In a prospective, randomized, double-blind, controlled clinical trial Demirozogul E. et al. compared the efficacy of paracetamol and DEX in reducing musculoskeletal pain [16]. The pain reported by patients included pain in the shoulder, neck, back, knee and hip. Two hundred adult people were enrolled in the study. Patients were divided into two groups. One group received 50 mg of DEX and the other group 1000 mg of paracetamol intravenously. The pain was measured using VAS and NRS before drug administration and at 15, 30, and 60 minutes. DEX was statistically more effective than paracetamol with all pain locations comparing the NRS and in 30 and 60 minutes from the start of the study comparing the VAS pain scale. There was a significant difference between DEX and paracetamol in back pain. Based on the results of the studies, it was found that DEX showed a better analgesic effect in all pain locations compared to paracetamol [16].

Cimen U. et al. compared intravenous DEX with paracetamol for the treatment of sore throat pain in a randomized, prospective, controlled, double-blind study [17]. Two hundred adult patients were enrolled in the study and divided into two groups. Ninety eight patients were given 50 mg of DEX and 102 1000 mg of paracetamol. Patients were assessed using the Difficulty Swallowing Scale (DSS), Throat Swelling Scale (SwoTS), the Sore Throat Relief Scale (STRS) and the Sore Throat Intensity Scale (STPIS). at 15, 30, 45, 60, 90, and 120 minutes from taking the medicine. There was no significant difference between groups in terms of the mean DSS, SPIS, SwoTS, and STRS scores at the examined time points. Both drugs reduced the sore throat equally [17].

Yavuz E. et al. conducted a randomized, single-center, double-blind, controlled trial in which they assessed the safety and efficacy of intravenous metoclopramide 10 mg, DEX 50 mg and metoclopramide 10 mg in combination with DEX 50 mg in the treatment of acute migraine attacks [18]. The study involved 150 adult patients who were randomly divided into 3 groups, 50 people each. The pain was measured by VAS at baseline and 15 and 30 minutes. Metoclopramide / DEX treatment had better results at 30 minutes than metoclopramide and DEX alone. No side effects were observed in any of the treatment groups [18].

Researchers compared DEX and lidocaine in 2021. Gur et al. treated migraine attack by intravenous lidocaine and DEX in a prospective, randomized, double-blind study [19]. The study involved 100 adult patients, who were divided into two groups of 50 people

each. First group received an 1.5 mg/kg lidocaine bolus and a 1 mg/kg infusion (first 30 min), followed by a 0.5 mg/kg infusion for a further 30 min intravenously. The needles with painkillers into the skin. That therapy has a local effect by stimulating a reflex action by increasing endorphin levels and by analgesic effect of the drug [23]. Akbas et al. in a prospective randomized study treat low back pain by mesotherapy or DEX. The study involved 104 adult patients, who were divided into two groups of 52 people each. First group received a minimum of 50 injections (with 2mg thiocolchicoside, 16.2mg lidocaine, 5mg tenoxicam) performed to each patient in the selected area, located from L1 vertebra to S1 vertebra vertically, and within 3–4 cm left side and 3–4 cm right side of the processus spinosus horizontally. The second group received intravenous injection of 50 mg DEX. Pain measurement was performed with VAS at 0, 15, 30 and 60 minutes and 24th hour. The decreases in pain intensity were statistically significantly higher in the mesotherapy group for all time intervals. Researchers followed-up the patients for 1 week after the treatment for the presence of any adverse effects. There was no statistically significant difference in having any side effects between study groups [24].

Mesotherapy is better than DEX in treating low back pain. A prospective randomized trial showed that mesotherapy is better than DEX in migraine without aura treatment [23]. The study involved 148 adult patients, who were divided into two groups. First group (76 people) received mesotherapy into the periparotid region, the glabella, and the area between the eyes and ears (2mg thiocolchicoside, 16.2mg lidocaine, 5mg tenoxicam), and to the area of the head where the pain occurred (such as frontal, parietal, occipital region: 16.2mg lidocaine, 5mg tenoxicam) for each patient. The second group (72 people) received intravenous injection of 50 mg DEX. Pain measurement was performed with VAS at 0,30,60,120 minutes and 24 hours after treatment. Researchers noted side effects and the patients that revisited the emergency department within 72 h. The decreases in pain intensity were statistically significantly higher in mesotherapy group for all time intervals. Adverse effects were minimal and similar in the study groups [23].

Moore R.A. et al. conducted a randomized, double-blind, double-sham, placebo-controlled study in parallel groups [25]. The efficacy and safety of orally administered DEX (12.5 mg, 25 mg) in combination with tramadol hydrochloride (TRAM) (37.5 mg, 75 mg) in four different combinations with defined ratios (DEX12.5 / TRAM37.5; DEX12.5/ TRAM75; DEX25 / TRAM37.5; DEX25 / TRAM75) and single components (DEX12.5; DEX25; TRAM37.5; TRAM75) with 400 mg of ibuprofen, which served as an active control and placebo-controlled for the treatment of moderate to severe pain after mandibular third molar extraction. Six hundred and six patients aged 18-64 participated in the study. As a rescue medication, 4 g of paracetamol was used, which was administered on-demand one hour after the study drugs were taken. The assessment of pain intensity (PI) and the assessment of intensity and pain relief (PAR) were measured according to the VRS before drug administration, and then after 15, 30 and 45 minutes, and after 1,1.5,2,2.5,3,3.5,4,5,6,8,12, and 24 hours from the moment of drug administration. The PI and PAR results estimated total pain relief (TOTPAR) and summed pain intensity differences (SPID) at 4, 6, 8, and 12 hours post-dose. Percentages of the theoretical maximum possible TOTPAR (% max TOTPAR) and SPID (% max SPID) were also estimated. The patient's overall assessment of the study drug (PGE – patient global evaluation) was performed 24 hours after the end of the study. If the patient took a rescue medication before 24 hours, the PI, PAR, and PGE assessments were made immediately before taking the rescue medication. Based on the time course of the mean values of PI and PAR values within 24 hours from the initiation of therapy, it was noticed that administration of DEX as monotherapy or in combination with TRAM quickly relieves the onset of pain. The use of DEX/TRAM resulted in greater pain relief for longer and greater peak pain relief. The proportion of subjects with ≥50% maximum total pain relief within 4 hours after dosing was greater than placebo for both doses of DEX and all DEX/TRAM combinations. However, within 6 hours after drug administration, the percentage of such people remained higher for 25 mg of DEX and all DEX/TRAM combinations.

After 8 hours, the patient response rate was higher than placebo for DEX25/TRAM75, DEX12.5/TRAM75, DEX25/TRAM37.5, and DEX25, and after 12 hours for DEX25/TRAM75, DEX12.5/TRAM75, and DEX25/TRAM37.5. Most patients who achieved complete pain relief were in the group taking 25 mg of DEX in combination with 75 mg of TRAM. The analysis of summary efficacy measures (TOTPAR,% max TOTPAR, SPID, % max SPID) showed that all DEX/TRAM combinations and both doses of DEX outperformed placebo. The exception was 12.5 g of DEX over 12 hours. The time to rescue medication was longer for all treatments studied compared to placebo. The longest value was recorded in the case of DEX12.5/TRAM75 and DEX25/TRAM75. According to the patient's overall assessment, all treatments used in the study were better than placebo, with the highest score achieved with DEX25/TRAM75. A dose-response relationship was analyzed between the tested drugs and active control, which showed that DEX25/TRAM75 as the only combination turned out to be significantly better than 400 mg of ibuprofen. One person in the DEX12.5/TRAM75 group experienced "severe" sleepiness. The remaining side effects were classified as "mild" or "moderate" in severity. The study proved that DEX25/TRAM75 therapy is effective in relieving pain after extraction of the mandibular third molar and is characterized by a quick onset of action [25].

In another randomized, double-blind, double-sham, placebo-controlled parallel study, Moore R.A. et al. investigated the efficacy and safety of oral DEX (25 mg) in combination with TRAM (75 mg) compared to using these drugs alone in the treatment of acute, severe pain following abdominal hysterectomy [26]. The study involved 606 patients aged 25-73, who were randomly divided into six groups. The treatment time consisted of two phases. The first one was the single-dose phase (the first 8 hours after taking the first dose). This was followed by a multi-dose administration phase with patients taking a further 6 doses with an 8-hour interval between doses. As a rescue medication, metamizole was used, which was administered at the patient's request for the entire duration of the therapy. Over 3 days, the patients repeatedly rated pain relief, pain intensity during movement and at rest, and made an overall assessment of the drug used in therapy at the end of each phase of the study. Based on VAS and VRS, SPID and TOTPAR were calculated. The primary efficacy endpoint was the mean SPID at rest for 8 hours after the first dose (SPID8). It was

found that the use of DEX in combination with TRAM gives better results than the use of these drugs in monotherapy. Regarding VAS at rest, during the single-dose phase, DEX/TRAM performed better at each point in the study than when these drugs were used alone, except DEX/TRAM and DEX at the 1 hour time point. In contrast, during the multiple-dose phase, a lower mean pain intensity over 48 hours was noted, while at rest for DEX/TRAM compared to the individual components. Similar results were noted for VAS in motion within 48 hours. The results of the average SPID for 2, 4, and 6 hours at rest, as well as the analysis of the average SPID in motion and at rest within 24 and 48 hours, proved better results of DEX/ TRAM than both drugs separately.

The results of the mean% max. SPID at 2, 4, 6, 8, 24, and 48 hours, during rest, proved that the therapy with DEX in combination with tramadol was more effective than the therapy with single components. Similar results were obtained as a result of the analysis of the mean% max. SPID at rest for 2, 4, 6, 8, 24, 48 hours and in motion during 24 and 48 hours.Combination therapy at all time points outperformed monotherapy with VRS during the single-dose phase except DEX/TRAM over DEX at the 3 hours time point. The analysis of mean TOTPAR values in 2, 4, 6, and 8 hours confirmed the superiority of DEX/TRAM over the use of these drugs separately. It was noted that in the DEX/TRAM group the time to first rescue medication was longer than in the monotherapy groups, and the proportion of patients who took the rescue medication within 24 and 48 hours was lower in the combination therapy group.

In terms of PGE, it was noted during the single-dose phase that DEX/TRAM was found to be statistically superior to single drugs. Adverse reactions were reported in 9.4% of DEX/TRAM patients, 15% of DEX patients, and 13% of TRAM patients. 1.8% of people reported a total of 15 serious side effects, one of which (psychotic disorder) in the DEX/TRAM group were considered treatment-related. The results of the studies showed that DEX25/TRAM75 showed better efficacy in the treatment of acute pain than the individual components after a single dose and a lasting effect after taking multiple doses of the drug [26].

Romero-Alejo E. et al. conducted a preclinical study in mice to evaluate the effectiveness of DEX in combination with TRAM and both drugs separately in the treatment of delayed latent pain sensitization and postoperative hyperalgesia (POH) [27]. 8-week-old male Swiss CD1 mice weighing 25-30 g were used for the study (4 groups with 10-12 animals each). A longitudinal plantar incision of the right hind paw was made under anesthesia, the plantar muscle was exposed, a longitudinal incision was made and the wound was closed. This action resulted in stress and mild or moderate pain in the injured paw lasting five days. Mice were divided into groups and administered DEX/TRAM in a 1:1 ratio, DEX, TRAM, or saline. One dose of DEX administered during the operation prevented postoperative hyperalgesia in 4 hours. and 1-2 days after surgery, while one dose of tramadol - within 4 hours. and 1 day. DEX inhibited POH more strongly than tramadol. On day 20, the animals were injected subcutaneously with saline, and on day 21 with naloxone, which induced hyperalgesia similar to that developed during postoperative hyperalgesia. No changes were observed as a result of the administration of saline, while the administration of naloxone resulted in the development of hyperalgesia to a similar extent in the groups receiving DEX and saline. In contrast, in the TRAM group, treatment with this drug prevented naloxone-induced hyperalgesia matter what the initial PI was [29].

Meloncelli S. et al. in 2020, conducted a study evaluating the efficacy and tolerability of oral DEX25/TRAM75 versus the intramuscular use of DS75/thiocolchicoside4 in the treatment of acute low back pain [30]. Eighty two adult patients participated in the study, 44 of whom were taking DEX/TRAM and 38 were taking DS/thiocolchicoside. The primary efficacy endpoint was the change in pain intensity at rest at days 1, 3, and 7 from the start of the study. Patients rated PI using the 11-point NRS scale. Secondary endpoints were: SPID on study day 7, number of people who achieved PI reduction during the study, and change in Doleur Neuropathique score (DN4) on the last study day from baseline. 1000 mg of paracetamol served as a rescue medication. DEX/TRAM therapy resulted in a gradual reduction of the mean pain intensity during the study and provided more durable and stronger analgesia on the 3rd and 7th day of treatment compared to DS/thiocolchicoside. The analgesic efficacy in the DS/thiocolchicoside group did not change over time, no improvement in the parameters was noticed after the first day of using this therapy. More patients in the DEX/TRAM group achieved at least a 30% reduction in PI compared to the DS/thiocolchicoside group. On Day 7, patients in the DEX/TRAM group outperformed patients in the DS/thiocolchicoside group in terms of a ≥50% reduction in PI. Higher SPID scores were noted for the group of patients taking DEX/TRAM. Patients in the DEX/TRAM group had a significantly lower reduction from baseline in DN4 compared to patients in the DS/thiocolchicoside group. There were no significant differences in the use of rescue medication between groups. No serious side effects were reported during the study. Based on the results of the study, it was concluded that DEX/TRAM may be an effective and valuable treatment for pain in patients with acute low back pain. Both treatments were well tolerated by the patients [30].

Cigerim L. and Kaplan V. conducted a randomized, double-blind clinical trial in which they assessed the efficacy of DEX and DEX in combination therapy with thiocolchicoside in two different proportional combinations in the treatment of pain after extraction of an impacted third molar [31].

The study involved 71 patients aged 18-36, who were divided into 3 groups. Patients in the first group (24 people) received 25 mg of DEX in combination with 4 mg of thiocolchicoside. Twenty three people in the second group received 25 mg of DEX in combination with 8 mg of thiocolchicoside, and 22 patients in the third group received 25 mg of DEX. The drugs were administered to the patients in each group twice a day from the end of the first hour after the operation. An additional drug in the case of pain was 500 mg of paracetamol. The pain was rated at 1,2,3,6,8, and 24 hours and on days 2, 3, and 5 using a VAS. There were no statistically significant differences in the mean VAS scores after 1,2,3,6, and 8 hours and after 2, 3, and 5 days in the study groups, however, patients in the second group had lower mean VAS scores than patients in the DEX group. After 24 hours, mean scores on the VAS were higher in the DEX group compared to the DEX plus 8 mg group. There was no statistically significant difference in VAS scores between the first and second groups, and also

between the first and third groups after 24 hours. The highest mean results in all treatment groups were recorded at 8 hours.

There was a decrease in the mean results of the were evaluated. RCS and Spike percentage values were significantly lower and FMJ onset time values were significantly longer in DEX given groups (once 20 mg/kg or 40 mg/kg intraperitoneally) [34]. This study showed that DEX has an antiepileptic feature by increasing epileptic threshold and this effect increases as the dosage increases.

Erdil A. et al. in 2020, conducted a study that assessed the effect of DEX on WAG / Rij rats suffering from absence epilepsy. Twenty eight male rats, 24-26 weeks of age, were included in the study and were divided into 4 groups of seven animals each [35]. First group received placebo, second 5, third 25, and fourth 50 mg/kg, i.p DEX. Absence-like seizures and related psychiatric comorbidity were assessed. Before and after drug injection the electrocorticography (ECoG) recording was taken for 180 min. Anxiety-depression-like behavior was tested after drug injection and EcoG recording with the open field test for 5 min. Low dose DEX (5 mg/kg) reduced absence-like seizures, but higher doses 25 and 50 mg/kg DEX significantly increased the number and duration of spike-wave discharges percentage between 0 and 30 min. 5 mg/kg DEX can reduce the occurrence of seizures in a genetic absence animal model and may have positive effects on anxiety-like behaviors [35].

In the future DEX can be preferred for administering NSAIDs to epileptic patients. In recent years, several studies have been published suggesting the chemopreventive potential of K [36,37,38]. In several tumors researchers found an enhanced COX-2 expression and it suggests a role COX-2 in carcinogenesis.

In 2019 Çoban et al. developed PEGylated nanocochleate formulation containing imatinib and DEX (IMA-DEX PEG COH) against fibrosarcoma [38]. The drug was designed for oral administrations. In this study a mouse fibrosarcoma model was used. Study was performed on fibrosarcoma-bearing Balb-C male mice (5 groups of 5 animals each). Doses were adjusted so that each animal received 4.8 mg imatinib and 0.09 mg DEX daily. After 14 days of treatment new drug tumor size, histopathology, and tyrosine kinase receptor inhibition were assessed. In the IMA-DEX PEG COH group there was observed no neural cell division in the tumor stroma and reduction of tumor volume. The percentage of healing at the cellular level was the highest compared to the other groups. In the tissues no lymphocytic infiltration and no necrotic area were found. The IMA-DEX PEG COH group demonstrated the greatest tyrosine kinase receptor inhibition [38].

CONCLUSIONS

Our review shows that the preoperative administration of DEX orally can reduce the severity of immediate postoperative pain and preventive use of DEX is a good option after arthroscopy. The findings of the review confirm that DEX is a very good pain reliever that is more potent than paracetamol and diclofenac sodium. DEX has a similar effect to lidocaine and dexmedetomidine. Mesotherapy is better than DEX in treating low back pain and migraine without aura. DEX and tramadol with DEX and thiocolchicoside are very effective combinations of painkillers. DEX25/TRAM75 therapy is effective in relieving acute and postoperative pain. DEX/TRAM therapy is more effective than TRAM/paracetamol therapy in the treatment of acute pain. Combination of metoclopramide and DEX gave better results than the monotherapies. Scientists are working on long-acting DEX and are looking for new uses of DEX in epilepsy and oncology.

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