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Review Article

The Combination of Remifentanil + Dexamethasone Has Favorable Effects in Management of Pain after Cesarean Section: A Systematic Review

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ABSTRACT

Introduction: Concerning the use of remifentanil and dexamethasone drugs each alone in creating painless childbirth, and also in the process of facilitating childbirth to increase the pain as much as possible and minimize the complications and possibly help the progress of labor, we decided that the effect of dexamethasone in combination to investigate with remifentanil in the control of labor pain in this systematic review.

Methodology: In this review article, the keywords that were selected based on MeSh and searched based on them included Remifentanil, labor, pain, Dexamethasone, combination, acceptability, effectiveness, vaginal delivery, VAS, headache, surgical delivery, hemodynamically stable, and hemodynamically.

Results: The average pain intensity in the treatment groups was measured and evaluated on four occasions 30, 60, 120, and 180 minutes after the intervention. The results showed that the average numerical scale of pain intensity measurement based on VAS in the group receiving remifentanil and dexamethasone 30 minutes after the start of the intervention was equal to 6.06 and the average of the same scores in the group receiving remifentanil at the same time was 6.83.

Conclusion: The simultaneous use of remifentanil and dexamethasone is recommended in comparison to the use of remifentanil because it is safe for both mother and child and causes more favorable analgesia and fewer complications during childbirth.

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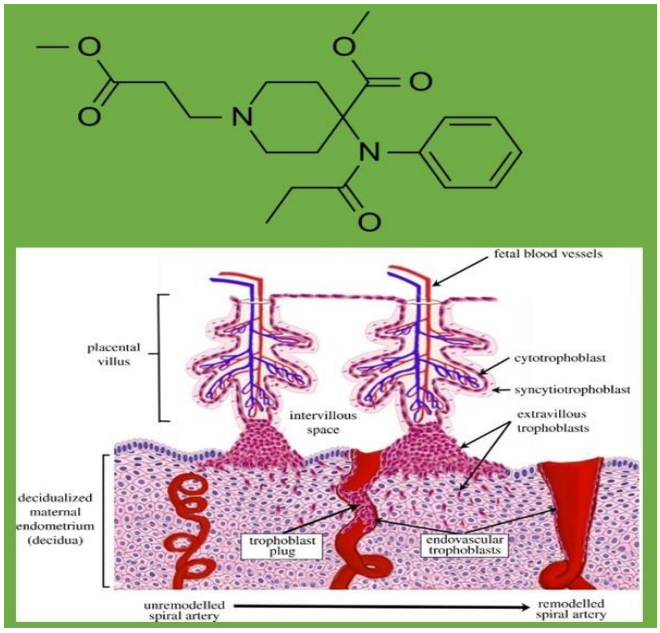
GRAPHICAL ABSTRACT



1- Introduction

Childbirth is a phenomenon during which regular uterine contractions begin and lead to the expulsion of the fetus and placenta [1-3]. Pain during childbirth and pregnancy is caused by uterine contractions, dilation of the cervix, and the perineum expansion [4-6]. The pain of childbirth is one of the excruciating pains that women experience throughout their lives. This pain is more intense and longer, especially in first-borns [7-9]. According to the studies, 77% of firstborns have described the pain of childbirth as severe and unbearable [10-13].

Side effects caused by labor pain in the fetus include: late drop in the fetal heart rate following the decrease in the mother's arterial oxygen pressure, decrease in uteroplacental blood flow (Fig. 1) due to the strong contraction of the uterus during labor pain, and fetal acidosis that occurs in some cases [14-16]. Therefore, it seems necessary to evaluate cheap and safe methods that have less complications for the mother and the baby and require less use of specialist personnel in this field.

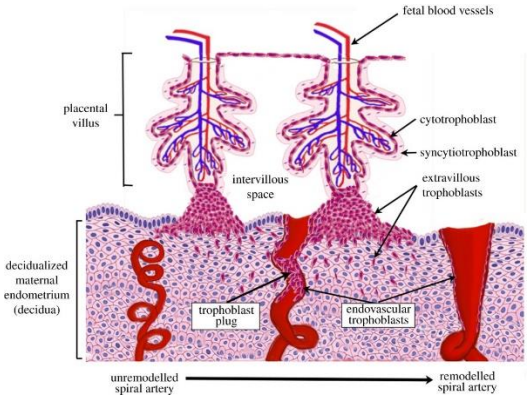


Fig.1. Uteroplacental blood flow.

All of these methods are divided into three groups such as psychological methods, local painkillers, and inhaled anesthetics [17-19]. Simple pharmaceutical methods include painkillers and narcotics, sedatives and amnestic drugs. One of the medicinal methods is the use of Remifentanil (Fig. 2).

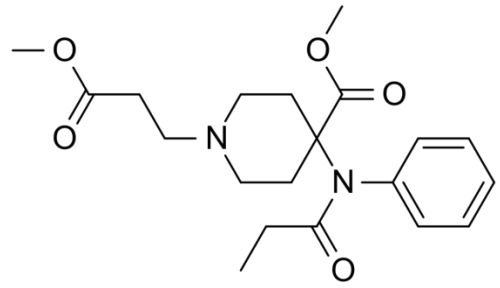


Fig. 2. Remifentanil molecule.

With the introduction of remifentanil as a fast-acting drug (the time to reach the peak effect after intravenous administration is 60 to 90 seconds) with immediate metabolism, the idea of using it in a pregnant mother with minimal effect on the fetus has attracted the attention of researchers [20-22]. Likewise, this drug is quickly metabolized by plasma esterases (Figure 3), despite the rapid passage of the placenta in the body of the fetus, and thus it has less adverse effects on the fetus. Remifentanil has an analgesic effect twice that of fentanyl and two hundred times that of morphine, and has an agonistic effect on opioid receptors [21-23]. It can also weaken respiratory and cardiac function and stiffness of skeletal muscles [24-26].

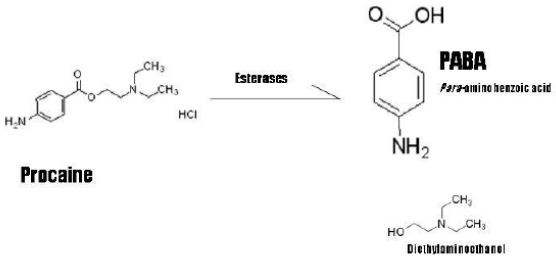


Fig. 3. Plasma esterases

The half-life of the drug is three to ten minutes. The onset of drug effect is 1 minute and the duration of its effect is 5 to 10 minutes after stopping the intravenous infusion. One of the drugs that may help prepare the cervix and the course of labor is the use of glucocorticosteroids. Although their role in the initiation of labor is not known, the finding of glucocorticosteroid receptors on fetal membranes at the beginning of the labor process has strengthened this role [۲۷]. According to the importance of the subject and given that the goal of midwifery is to emphasize natural and safe childbirth, it seems that one of the ways to achieve this goal is methods that, in addition to cause pain, also cause spontaneous labor to begin [28-30]. On the other hand, due to the increase in the rate of cesarean section due to the inappropriateness of the cervix and avoiding its high costs in medical systems, it is necessary to use effective and safe methods to prepare the cervix and induce labor [31-33].

Concerning the great emphasis that is placed on natural childbirth as the best method of childbirth today, and taking into account that experts believe that with the new techniques for painless childbirth, no pregnant woman should suffer severe pain during childbirth, as the rate of cesarean sections is only decrease due to mother's fear [34-36]. Given that the use of remifentanil and dexamethasone drugs each alone in creating painless childbirth, and also in the process of facilitating childbirth to increase the pain as much as possible and further minimize the complications and possibly help the progress of labor, we decided that the effect of dexamethasone in combination to investigate with remifentanil in the control of labor pain in this systematic review [37].

The DEX-2-TKA was a randomized, blinded, placebo-controlled, and multicenter trial in participants undergoing primary TKA conducted to investigate the dexamethasone effects on morphine consumption, levels of postoperative pain, and harm. The methodology has been described in detail in the primary publication (ref), the protocol article and in the statistical analysis plan. In brief, the trial was conducted at one private and four public Danish hospitals. Patients were randomized into one of three groups receiving either: Dexamethasone + placebo, dexamethasone + dexamethasone, or placebo + placebo in a 1:1:1 ratio. The first dose

of trial medication (intravenous dexamethasone 24 mg or placebo) was administered immediately after onset of anesthesia. Twenty-four hours after end of surgery, the second dose (dexamethasone 24 mg or placebo) was administered.

As the two groups receiving preoperative dexamethasone were identical at the time of outcome assessment for this post-hoc analysis, they were merged to one and were compared with placebo yielding a ratio of 2:1 between the groups receiving dexamethsone and the placebo group.

Patients received either spinal anesthesia or general anesthesia (remifentanil and propofol were preferred). Before end of surgery all patients received ondansetron iv 4 mg. For patients in general anesthesia, sufentanil (0.3 µg/kg) was administered. All participants were provided with a patient-controlled analgesia pump (morphine 1 mg/mL, bolus 2 mg, lock-out 6 minutes, no background infusion) for 24 hours, postoperatively. Additional boluses of 2 mg morphine on participant request were allowed the first hour after cessation of anesthesia. All participants received a protocolled non-opioid analgesic pain alleviation regime comprised of oral paracetamol 1 g and ibuprofen 400 mg given 1 hour before and every 6 hours after surgery and the surgeon administered local infiltration analgesia intraoperatively according to a standardized regimen.

2- Methodology

In this review article, all databases including Google Scholar, Scopus, Web of Science, PubMed, SID, MagIran, and the Cochrane Library were searched and reviewed by both authors of this article based on PRIZMA guidelines without time and language limitations. The keywords that were selected based on MeSh and searched based on them included Remifentanil, labor, pain, Dexamethasone, combination, acceptability, effectiveness, vaginal delivery, VAS, headache, surgical delivery, hemodynamically stable, and hemodynamically. These keywords were determined by both authors in one meeting, and then the search was performed in the mentioned databases by each author separately. The glucocorticoids effects may include both genomic and rapid nongenomic effects. The potential rapid analgesic effect during surgery has not previously been investigated. We aimed to explore the effect of dexamethasone on intraoperative infusion rate of remifentanil in patients undergoing total knee arthroplasty (TKA) surgery under general anesthesia.

The search process is given in the following:

Table 1. Search strategy in PubMed database based on MeSh criteria

(Remifentanil [mh] OR Dexamethasone [tiab] OR effectiveness [tiab]) AND (vaginal delivery [mh] OR VAS [mh] OR headache [tiab] OR Local Anaesthesia [tiab] OR Regional Anesthesia [tiab] OR Cesarean Section [tiab] OR C-Section [tiab] OR Cesarean Birth [tiab] OR Surgical Delivery [tiab] OR Hemodynamically Stable [tiab] OR hemodynamically [tiab].

The inclusion criteria of studies in this present study included the following:

1. The time limit was not applied.
2. Language restriction was not applied.
3. The studies had clear results.
4. The studies had a prospective approach.
5. The studies were in the form of clinical trials.
6. Randomization was done for all studies.
7. The study should be single-blind or double-blind.
8. The results of the study are expressed without bias.
9. Studies should be of good and high quality.

The criteria for excluding studies from the present study included the following:

1. Case studies, reviews, reports of rare cases, letters to the editor, and descriptive.
2. The age of the participants should be less than 18 years old.
3. The method of randomization is not clearly stated.
4. The dosage of the drugs used are not stated.
5. There is no control group in the study.
6. The expected results have not been achieved.
7. Exclusion criteria have not been stated.
8. The intervention method is not clearly mentioned.
9. The conclusion is ambiguous.

All the studies in the initial search were evaluated according to the inclusion and exclusion criteria, and if they met the necessary criteria, they were included in the evaluation. Then, the title and purpose of the study were reviewed and evaluated, and studies were included in the review that had a clear purpose in the title and were in line with our study. Finally, the full text of each article was reviewed by both authors, and the studies that had the appropriate and desirable quality were included in this systematic review. All the important information of each article was written and recorded separately by both authors in a paper sheet, and then in a face-to-face interview, the important information was discussed, and finally the important information of each article was included in this study.

3- Results and Discussion

In this study, pain intensity was measured based on VAS before the intervention. Statistical results using Mann-Whitney test showed that there is no significant difference between patients in two treatment groups. The average pain intensity in treatment groups was measured and evaluated on four occasions 30, 60, 120, and 180 minutes after the intervention (Figure 3). The results revealed that the average numerical scale of pain intensity measurement based on VAS in the group receiving remifentanil and dexamethasone 30 minutes after the start of the intervention was equal to 6.06 and the average of the same scores in the group receiving remifentanil at the same time was 6.83. The statistical results showed that this difference is significant in the treatment groups.

Also, the results showed that the average pain intensity 60 and 120 minutes after taking the drug in the treatment groups has a significant difference. The results showed that the pain intensity in the 180th minute after the intervention was significant between both groups. After calculating and analyzing the data, it was observed that the average length of active labor phase in the group receiving remifentanil is longer than the group receiving remifentanil and dexamethasone. The distance and length of uterine contractions were recorded three times in a row before drug injection and twice in a row after taking the drug every 15 minutes to one hour. There was no significant difference in the mean duration and interval of uterine contractions after taking the drug compared to before the injection in both groups in the Mann-Whitney test. In this study, side-effects such as headache, dizziness, drowsiness, restlessness, nausea, hallucinations, and delusions were evaluated. The results showed the complications between two groups based on nausea, vomiting, and headache (Figure 4).

The degree of pain reduction in the group receiving remifentanil and dexamethasone was significantly lower than the group receiving remifentanil at all measurement points after taking the drug, which could be due to the analgesic effects of dexamethasone [37-39]. A study entitled: “Comparing the effectiveness of Entonox gas alone and in combination with dexamethasone in the control of labor pain” was conducted, it showed that the pain score in patients who took Entonox and dexamethasone was significantly lower than the opposite group and dexamethasone improved the analgesic effects [40-42].

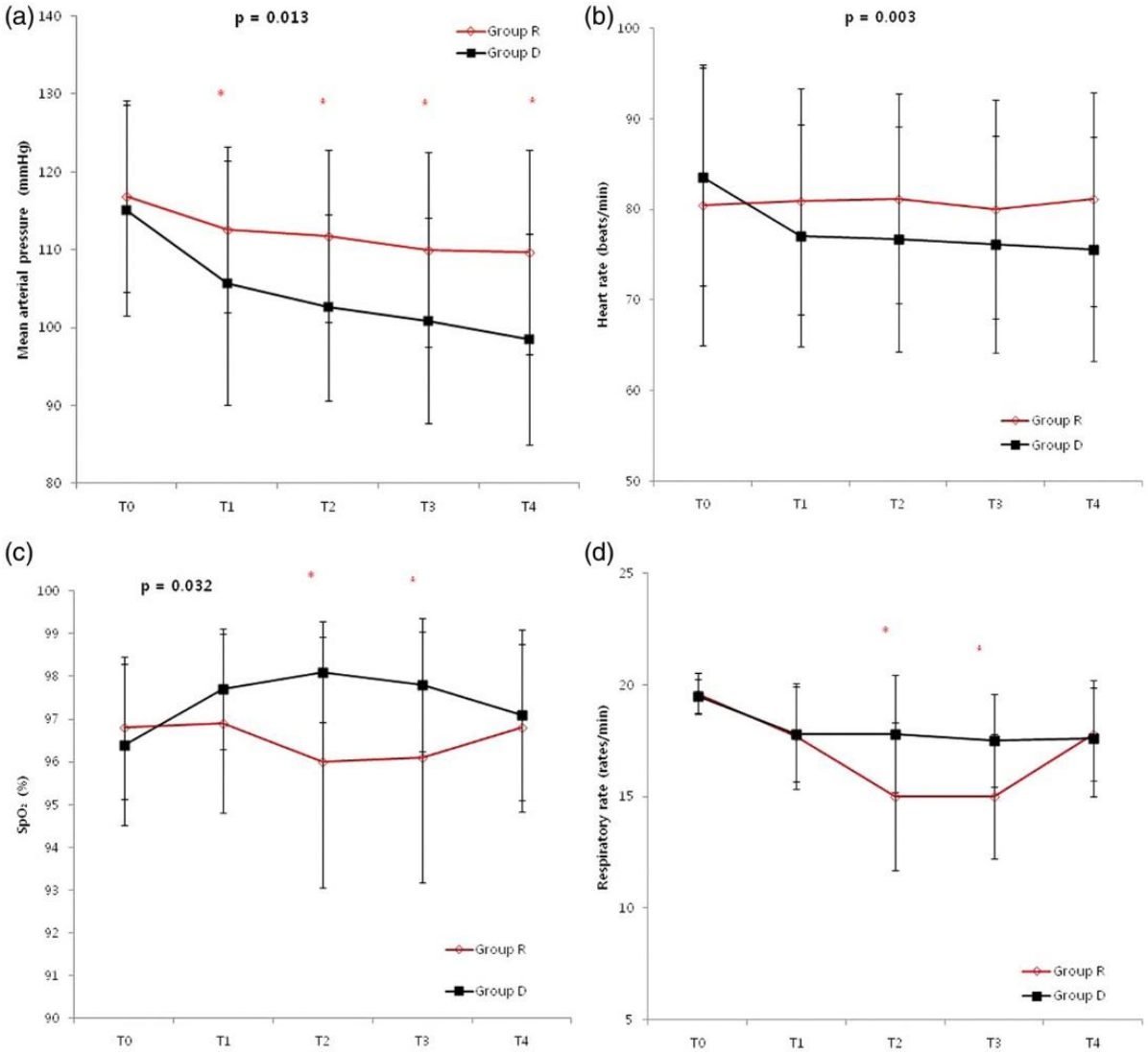


Figure 3. Hemodynamic in two groups.

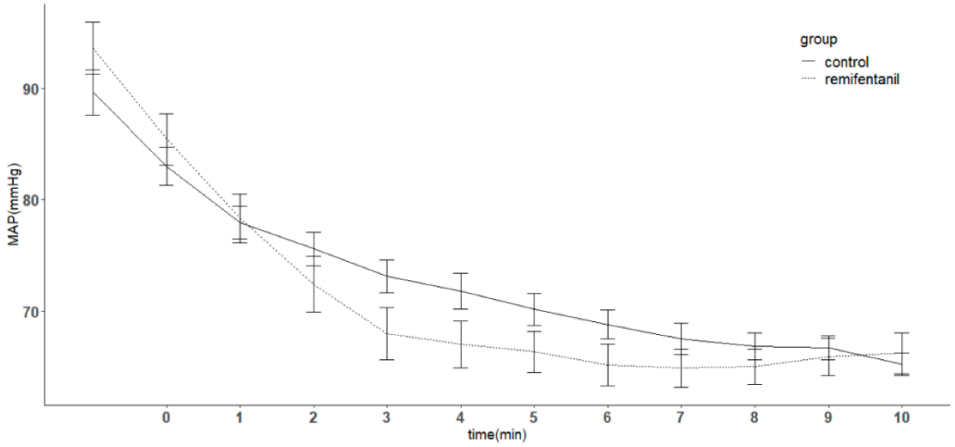


Figure 4. Complication between two groups.

A study aimed at the analgesia of remifentanil in 41 pregnant women was investigated [43]. The pain score decreased significantly in the first 3 hours and at the end of the first and the second stages of labor [44-46]. The sedation of the mother was moderate and the condition of the babies was reassuring. Studies have shown that at the end of pregnancy, with an increase in cortisol, prostaglandins derived from the amnion and chorion are metabolized and easily affect the adjacent decidua and myometrium. In other words, they cause the transition from uterine phase zero to phase one and two of labor [47-49]. It seems that dexamethasone administration has a positive effect on the preparation of the cervix through the improvement of the Bishab score, which reduces the time interval between induction and delivery, as well as accelerates delivery. Therefore, by activating the biochemical cascade of childbirth, dexamethasone can shorten the latent phase and accelerate and progress childbirth [50-52]. The results of the study showed that the Apgar score of the first and fifth minutes of the fetus and maternal and fetal complications including chorioamnionitis and neonatal sepsis in both groups using dexamethasone and normal saline to induce labor had no statistically significant difference [51-53]. In the present study, nausea, vomiting, and headache in the group using remifentanil had a significant difference with the group receiving remifentanil and dexamethasone, and in other drug side effects, no significant difference was observed between both groups, and this shows that by adding Dexamethasone can reduce the side-effects and achieve a safer method [54-56]. The results of a study showed that adding dexamethasone to Entonox significantly reduces nausea and vomiting [57].

4- Conclusion

The simultaneous use of remifentanil and dexamethasone is recommended in comparison with the use of remifentanil because it is safe for the mother and child, and also causes more favorable analgesia and fewer complications during childbirth. Among the limitations of this research, we can point out the financial limitations to select a larger statistical population, limitations in diagnosis, and limitations in separating the stages of active phase of labor in terms of pain intensity. Therefore, a study with a larger statistical population and separating the stages of labor and delivery is recommended. If possible, the blood concentration of narcotics should be measured.

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