SUCCINYLCHOLINE-INDUCED MYALGIA IN OBSTETRIC PATIENTS SCHEDULED FOR CAESAREAN SECTION

- Diclofenac vs Placebo Patches -

MOJGAN RAHIMI*, JALIL MAKAREM**
AND AFSHIN GOSHTASBI GOHARRIZI**

Abstract

Background: Succinylcholine -induced myalgia is a minor but frequent complication. Its incidence and severity is different according to the studied population. The aim of this study was evaluation of the diclofenac patch effect on postoperative succinylcholine -related myalgia in cesarean section.

Methods: The study was a prospective randomized double blind, placebo-controlled trial. One hundred twenty six participants undergoing elective cesarean section (previous cesarean section) were randomized in two equal groups (63 participants in each): the diclofenac patch (containing 180 mg of diclofenac epolamine salt) and the placebo. Surgery was performed following rapid sequence induction of general anesthesia. All patients were paralyzed for intubation by succinylcholine (1.5 mg/kg). Data on baseline characteristics, fasciculation, postoperative myalgia (at 12, 24 and 48 hours after operation), the need to analgesic agents, and adverse effects of diclofenac patch were collected.

Results: The basic characteristics were comparable between the two groups. The severity of fasciculation did not significantly vary between two groups. In diclofenac group, the incidences of myalgia at 12, 24 and 48 hours after operation were 23.8%, 19.1%, and 12.7% respectively versus incidences of 52.4%, 47.6%, and 44.4% respectively in placebo group. The incidence and severity of myalgia were significantly lower in patients receiving diclofenac through three evaluation periods (all p values less than 0.01). No participants left the study because of the complications.

Conclusion: Diclofenac patch is effective and safe in the prevention of postoperative succinylcholine induced myalgia after cesarean section.

Keywords: Succinylcholine, postoperative complications, myalgia, diclofenac

---

From Department of Anesthesiology and Intensive Care, Imam Khomeini Medical Center, Tehran University of Medical Sciences.

* MD, Assis. Prof. of Anesthesiology.

** MD, Resident in training of Anesthesiology.

Corresponding author: Jalil Makarem M.D., Department of Anesthesiology and Intensive Care, Imam Khomeini Medical Center, Keshavarz Blvd., Tehran 1419733141, Iran. Tel/Fax: 00982166438634. Email j _makarem@razi.tums.ac.ir

Financial Support: Authors themselves have provided all financial support for this study.

Conflict of Interest: There is no conflict of interest.

Introduction

Succinylcholine remains the drug of choice during rapid sequence induction of anesthesia in many countries[1]. Fasciculation and myalgia are minor but frequent adverse effects of succinylcholine administration. Myalgia, which can be accompanied by muscle stiffness, can last for several days and at least in some patients, can induce significant discomfort[2]. In females, postoperative myalgia (POM) is more frequent than males[3] and early ambulation is associated with higher incidence and severity of succinylcholine -induced POM[4].

In our country, Iran, the use of general anesthesia still prevails for cesarean section because of patient's request, succinylcholine is used almost always as a muscle relaxant in this condition. Therefore, POM is a frequent problem. The incidence of myalgia at the first 24 hours after operation has been reported from 10 to 83%[5]. In a recently published study, POM was important to eighty-nine percent of patients, and they requested to be avoided[6].

The topical application of non-steroidal anti-inflammatory drugs (NSAIDs) were effective in decreasing both acute and chronic pain[7], but the evidence supporting the use of transdermal NSAIDs to alleviate succinylcholine -induced myalgia is limited[8].

The aim of this study was to determine if the application of diclofenac patch at the beginning of the cesarean section could prevent succinylcholine -induced POM.

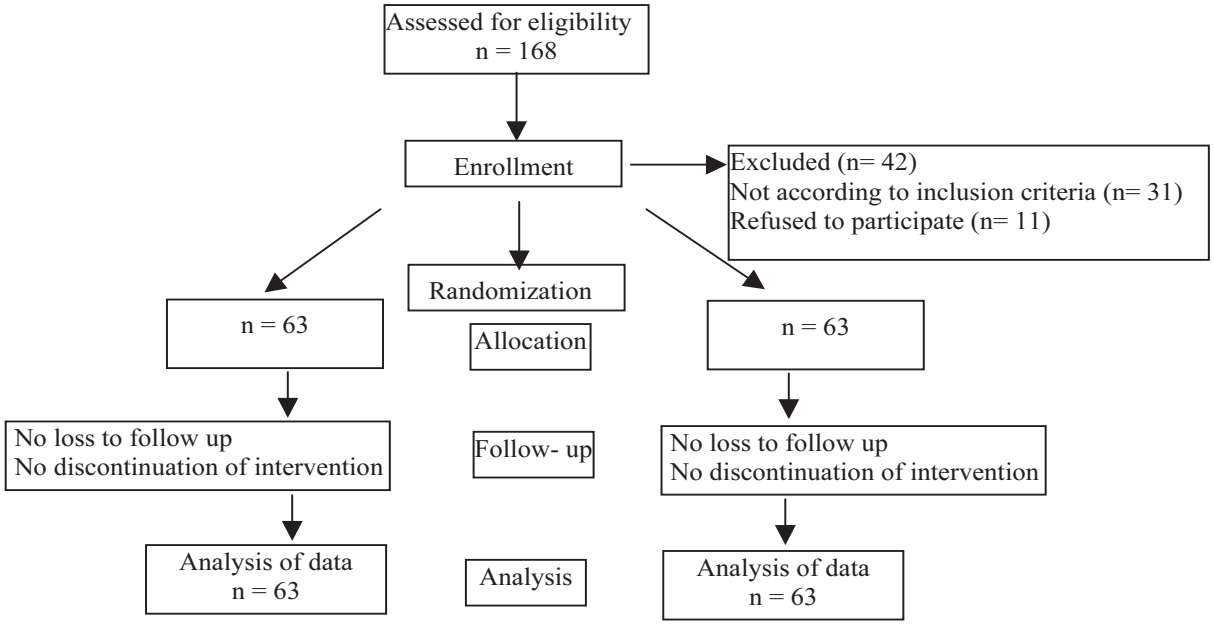
Methods and Materials

The study was performed from May to December 2008 in a referral educational hospital. The protocol was approved by our University Ethics Committee. Informed consent was obtained from all participants before enrollment in the study. We conducted this study to evaluate the hypothesis that diclofenac patch can prevent or reduce postoperative myalgia (POM).

Participants were ASA I or II, scheduled for repeated cesarean section (elective surgery) and had refused regional anesthesia. They were included in this prospective, randomized, double blinded, placebo controlled study. The history of asthma, smoking, known hypersensitivity to NSAIDs, coagulopathy, anticipated difficult airway, evidence of preeclampsia, history of gastrointestinal bleeding, significant liver or renal disease, history of psychological disorders, steroid consumption, and recent upper respiratory tract infection or irritation, were the exclusion criteria.

One hundred twenty six participants were randomly allocated in two equal groups of 63: diclofenac patch group or placebo patch group (Fig.1).

Fig. 1 Trial profile of the 168 participants



Randomization was done by computerized random numbers. The anesthesiologist and the participants were not aware of the allocation.

Following pre-oxygenation, rapid sequence induction of general anesthesia consisted of thiopental sodium (5 mg/kg) and succinylcholine (1.5 mg/kg). Maintenance of anesthesia was preserved with isoflurane 0.6% in combination with nitrous oxide 50% in oxygen. Atracurium (0.2 mg/kg) was administered as maintenance of muscle relaxant. Fentanyl (2 µg/kg, i.v.), midazolam (0.03 µg/kg, i.v.), meperidine (1mg/kg, i.v.) were administered after clamping of the umbilical cord. Neuromuscular blockade was reversed by neostigmine (40 µg/kg) and atropine (20 µg/kg) intravenously at the end of the procedure.

Postoperative care was standardized for all patients. For post operative analgesia patients received vaginal suppository of diclofenac sodium (50 mg every 8 hours). Pain related to surgical intervention was treated with meperidine (1 mg/kg i.v.), if not controlled by diclofenac suppository meperidine is considered a rescue analgesia). Intramuscular injection was not performed during the preoperative or postoperative period.

Diclofenac epolamine patch (Flector® Tissuegel, IBSA, Switzerland) consists of 1.3% diclofenac epolamine (Equivalent to 1% diclofenac free acid or 180 mg of diclofenac epolamine) in a hydrophilic adhesive applied to a non woven polyester felt backing. Surface area of diclofenac patch was 140 cm^2 (the patch was 14 cm long and 10 cm wide). The placebo patch (supplied by Daru pakhsh, Tehran, Iran) was indistinguishable from the diclofenac patch. Diclofenac or placebo patch were applied to the posterior skin of the neck 30 minutes before the induction of anesthesia. Patches were removed 12 hours later.

The incidence and severity of postoperative fasciculation and myalgia were the main outcomes of the study. Fasciculation was recorded based on a four-point rating scale: a)no fasciculation, b)mild: fine fasciculation of the eyes, face, neck, or fingers but without limb movement c)moderate: fasciculation involving limbs and trunk, d) severe: fasciculation requiring a forceful retention[9]. Muscle pain not related to the surgical intervention was graded according to Kararmaz et al[10]: absence of muscle pain = no myalgia (0 points); minor stiffness limited to one area of the body = mild(1 point); muscle pain or stiffness noticed spontaneously by the patient, which may require analgesic therapy = moderate(2 points); and generalized, severe, or incapacitating discomfort = severe(3 points).

Myalgia data were gathered by a trained nurse who was blinded to the patches; 12, 24, and 48 hours after operation. Adverse effects on the digestive system and skin, if any, were noted, by the nurse. Excessive postoperative bleeding was supposed to be related to impairment of platelet function.

In our pilot study (on 10 participants), the incidence of POM was 60%. Our goal was to achieve a minimum of 50% decrease in the frequency of myalgia. With a power of 90% and a significance level of 0.05, we calculated that 63 participants were required in each group.

Participants' characteristics such as age, weight and duration of anesthesia were compared by using student's T-test. Chi square test was used to identify differences in the incidence of myalgia and the need to rescue analgesia. Difference in the severity of myalgia was compared by using Mann Whitney U-test. SPSS software version 16 (SPSS, Inc., Chicago, ILL) was used for statistical analysis. P values < 0.05 was considered as statistically significant.

Results

In the 126 participants studied, no loss to follow up occurred. Basic characteristics were comparable between two groups. Scale of fasciculation was similar in both groups (Table 1).

Table 1
Patients' basic characteristics

Variable*	diclofenac (n =63)	placebo (n =63)
Age(years)	27.5 ±6.4	26.8 ±7.8
Weight (kg)	68.7 ±5.3	69.6 ±4.1
Duration of anesthesia (min)	49.2 ±4.7	51.3 ±6.1
Severity of fasciculation (no/mild/moderate/severe)	2/43/16/2	3/45/14/1

*values are mean ± standard deviation (SD) or number. All p values were >0.05.

Table 2
Comparison of myalgia in the two groups

	diclofenac (n =63)	Placebo (n=63)	P value (for incidence)	P value (for severity)
12 hours postop.				
No	48 (76.2)	30 (47.6)	0.002	<0.001
Mild	10 (15.9)	9 (14.3)		
Moderate	4 (6.3)	19 (30.2)		
Severe	1 (1.6)	5 (7.9)		
24 hours postop.				
No	51 (80.9)	33 (52.4)	0.001	<0.001
Mild	10 (15.9)	16 (25.4)		
Moderate	2 (3.2)	13 (20.6)		
Severe	0	1 (1.6)		
48 hours postop.				
No	55 (87.3)	35 (55.6)	<0.001	<0.001
Mild	8 (12.7)	21 (33.3)		
Moderate	0	7 (11.1)		
Severe	0	0		

Values are number (percent).

In both groups, complaints from myalgia were in the neck or shoulder muscles or both. No distal limb or trunk myalgia was detected. Myalgia scores were compared between the two groups. Myalgia incidences and severities were significantly lower in diclofenac group in comparison with placebo group (Table 2).

Request for rescue analgesia was significantly more frequent in the placebo group (26.4% of participants versus 10.9% of participants, p = 0.005).

Adverse effects of patches were not significantly different between two groups (Table 3). No participants left the study because of the complications.

Table 3
The complications of patches in two groups.

	diclofenac (n = 63)	placebo (n = 63)
Skin (Pruritus, dermatitis) †	2 (3.2)	3 (4.8)
Gastrointestinal Disorders (dyspepsia, nausea)†	3 (4.8)	1 (1.6)

Values are number (percent).
† p values > 0.05.

Discussion

In this study, preoperative application of diclofenac patch significantly palliated the incidence and severity of succinylcholine induced post cesarean section myalgia.

Based on our search, transdermal application of NSAIDs for the prevention of POM had not been reported previously. However, there have been several reports to reduce POM with different medical interventions[5], but a few studies evaluated the effects of systemic NSAIDs. Naguib et al[11], compared lysine acetyl salicylate with the muscle relaxant atracurium 3 minutes before paralysis. Both groups were found to have a lower incidence and intensity of POM than control group, with no significant difference between treatment groups. Kahraman et al[12] showed that intramuscularly administered diclofenac was effective on prevention of suxamethonium-induced myalgia.

In this study we administered diclofenac hydroxyl ethyl pyrrolidine (DHEP), also known as diclofenac epolamine, that is a patented salt of diclofenac. This

salt of diclofenac exerts very peculiar characteristics differentiating it from other diclofenac salts as well as from other available NSAIDs. The main peculiar characteristic of this salt of diclofenac is its very high solubility in both lipidic and hydrophilic tissues which is not seen, in other NSAIDs[13]. These properties cause effective absorption in regional tissues with low but sustained circulating levels[14].

However, there are debates about inflammatory origin of succinylcholine induced myalgia[15,16], and several authors considered anti inflammatory mechanism for NSAIDs in lessening POM[11,12,17].There may be parallels between the calcium influx seen after succinylcholine and that observed in experimentally induced muscle damage. Lipo-oxygenase products are mediators of calcium induced intracellular enzyme efflux from skeletal muscle, whereas cyclo-oxygenase products may mediate myalgia. Prostaglandins produce further tissue damage, resulting in more pain and damage. The use of NSAIDs may interrupt this prostaglandin- mediated destructive cycle and this may provide a rationale for their use in preventing POM[2].

The analgesic actions of NSAIDs; Can be dissociated from anti-inflammatory effects and this may reflect additional spinal and supraspinal actions of NSAIDs to inhibit various aspects of central pain processing[18]. Low stable concentration of diclofenac with transdermal administration on this study may exert an effective analgesic action. On the other hand, high local concentration of diclofenac on the head and neck region may be effective on alleviating the postoperative neck and/or shoulder myalgia.

Fasciculation was not different between two groups in the study as the same as mentioned by others[5]. Diclofenac i.m. did not have any effects on severity of suxamethonium induced fasciculation, too (12). However, the relationship between fasciculation and POM has not been well defined[2,5] In this study, no significant complications had occurred by application of diclofenac patch, as previously reported by Rahimi et al[19].

Measurement of serum levels of inflammatory and anti-inflammatory cytokines can help to clarify the pathophysiologic mechanisms of succinylcholine induced myalgia and the effects of transdermal NSAIDs, especially diclofenac patch.

It can be concluded that application of preoperative diclofenac patch is effective and safe in the prevention of POM in cesarean section.

Acknowledgements

Authors themselves have provided all financial support for this study. We give warm thanks to Shohre Alavi for her text editing.

References

1. Morris J, Cook TM: Rapid sequence induction: a national survey of practice. *Anaesthesia*; 2001, 56:1090-1115.
2. Wong SF, Chung F: Succinylcholine-associated postoperative myalgia. *Anaesthesia*; 2000, 55:144-152.
3. Riding JE: Minor complications of general anaesthesia. *Br J Anaesth*; 1975, 47:91-101.
4. Oxorn DC, Whatley GS, Knox JWD, Hooper J: The importance of activity and pretreatment in the prevention of suxamethonium myalgias. *Br J Anaesth*; 1992, 69:200-201.
5. Schreiber JU, Lysakowski C, Fuchs-Buder T, Trame' R MR: Prevention of succinylcholine-induced fasciculation and myalgia: A meta-analysis of randomized trials. *Anesthesiology*; 2005, 103:877-884.
6. Allen TK, Habib AS, Dear GL, White W, Lubarsky DA, Gan TJ: How much are patients willing to pay to avoid postoperative muscle pain associated with succinylcholine. *J Clinic Anesth*; 2007, 19:601-608.
7. Moore RA, Tramer MR, Carrol D, Wiffen PJ, Mcquay H: Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. *BMJ*; 1998, 316:333-338.
8. Cohen SP, Mullings R, Abdi S: The pharmacologic treatment of muscle pain. *Anesthesiology*; 2004, 101:495-526.
9. Mencke T, Schreiber JU, Becker C, Bolte M, Fuchs-Buder T: Pretreatment before succinylcholine for outpatient anesthesia. *Anesth Analg*; 2002, 94:573-576.
10. Kararmaz A, Kaya S, Turhanoglus S, Ozyilmaz MA: Effects of high-dose propofol on succinylcholine-induced fasciculations and myalgia. *Acta Anaesthesiol Scand*; 2003, 47:180-184.
11. Naguib M, Farag H, Magbagbeola JA: Effect of pre-treatment with lysine acetyl salicylate on suxamethonium-induced myalgia. *Br J Anaesth*; 1987, 59:606-610.
12. Kahraman S, Ercan S, Aypar U, Erdem K: Effect of pre-operative Lm. Administration of diclofenac on suxamethonium-induced myalgia. *Br J Anaesth*; 1993, 71:238-241.
13. Fini A,Fazio G, Rapaport I: Diclofenac/N-(2hydroxyethil) pyrrolidine: a new salt for an old drug. *Drugs Exp Clin Res*; 1993, 21:81-88.
14. Assandri Acanali S, Giachetti O: Local tolerability and pharmacokinetic profile of a new transdermal delivery system, diclofenac hydroxyethylpyrrolidine plaster. *Drugs Exp Clin Res;* 1993, 21:89-94.
15. Schreiber JU, Mencke T, Biedler A, Furst O, Kleinschmidt S, Buchinger H, Fuchs-Buder T: Postoperative Myalgia After Succinylcholine: No Evidence for an Inflammatory Origin. *Anesth Analg*; 2003, 96:1640 -1644.
16. Mcloughlin C, Nesbitt GA, Howe JP: Suxamethonium induced myalgia and the effect of pre-operative adminstraion of oral aspirin. *Anaesthesia*;1988, 43:565-567.
17. Leeson-Payne CG, Nicoll JM, Hobbs GJ: Use of ketorolac in the prevention of suxamethonium myalgia. *Br J Anaesth*; 1994, 73:788-790.
18. Sawynok J: Topical and peripherally acting analgesics. *Pharmacol Rev*; 2003, 55:1-20.
19. Rahimi M, Makarem J: Effects of diclofenac epolamine patch on postoperative sore throat in parturients after cesarean delivery under endotracheal general anesthesia. *Acta Anaesthesiol Taiwan*; 2009, 47:17-21.