A Comparative Study to Evaluate Efficacy of Post-Operative Analgesia of Fentanyl Transdermal Patch Versus Ketoprofen Patch in Major Abdominal Surgeries Performed under General Anaesthesia in North Eastern India

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ABSTRACT

BACKGROUND

Safe & efficacious post-operative pain control is a significant aspect of patient treatment in the part of an anaesthesiologist. The present study was carried out to determine the efficacy and safety of fentanyl transdermal patch and ketoprofen patch for post-operative analgesia in major abdominal surgeries under general anaesthesia in a tertiary care teaching hospital in Assam, India.

METHODS

After ethical approval, 60 patients of either sex, aged between 18 - 60 years, American Society of Anaesthesiologists (ASA) physical status I or II posted for major abdominal surgeries under general anaesthesia were included in this prospective, single blinded, randomized, comparative study. The patients were randomly allocated to receive either ketoprofen transdermal patch (Group K n_1 = 30) or fentanyl transdermal patch (Group F n_2 = 30) 4 hours prior to the surgery. Pain was assessed post-operatively after an interval of every 4 hours for 24 hours using visual analogue scale (VAS), verbal rating scale (VRS). Sedation was assessed at same intervals post-operatively using Ramsay sedation scale.

RESULTS

During the first 4 and 8 hours following surgery, the difference in mean VAS, VRS observed between the two groups were found to be statistically non-significant ($p > 0.05$). Whereas, during 12 hours, 16 hours, 20 hours, and 24 hours following surgery, the difference in mean VAS, VRS observed between the two groups was found to be statistically significant ($p < 0.05$). No patient in fentanyl group had score of more than 3 in Ramsay sedation scale during the study. Rescue analgesia was required in 3 patients (10 %) of the ketoprofen group whereas no patient in fentanyl group needed rescue analgesia.

CONCLUSIONS

Fentanyl transdermal patch (25 mcg/hr) applied 4 hours prior to surgery, had an edge over ketoprofen transdermal patch (100 mg) in attenuating post-operative pain and showed comparatively longer duration of action, without showing any serious side effect.

KEY WORDS

Transdermal Ketoprofen, Fentanyl, Analgesia

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BACKGROUND

As defined by international association for pain (IASP), pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".[1]

Besides providing a painless surgery, it is the responsibility of the anaesthesiologist to ensure safe and effective analgesia post operatively. A good peri-operative physician should plan the post-operative analgesic regimen beforehand the surgery begins because an effective management of pain will allow easy recovery from tissue trauma or surgery and facilitate early overall recovery of the patient. Surgery causes local tissue injury with subsequent release of prostaglandins, serotonin, histamine, bradykinin, substance P, 5-hydroxytraptamine. Noxious stimuli, transduced by nociceptors, are transmitted to the neuroaxis by Aδ and C nerve fibres. The analgesics which are used frequently belong to different classes like non-steroidal anti inflammatory drugs (NSAIDs), opioids, glucocorticoids, local anaesthetics, α-2 agonists, ketamine and gabapentanoids. Most commonly these drugs are given orally or parenterally. In recent past, transdermal route of drug delivery is becoming very popular since it allows controlled absorption, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin. Ketoprofen, a NSAID, is an oxo monocarboxylic acid that consists of propionic acid substituted by a 3-benzoylphenyl group at position 2.[2]

The anti-inflammatory effects of ketoprofen are due to inhibition of cyclooxygenase-2 (COX-2), the enzyme involved in prostaglandin synthesis via the arachidonic acid pathway which results in decreased levels of prostaglandin thereby reducing pain, inflammation and fever. Ketoprofen is a non-specific COX inhibitor. Inhibition of COX-1 confers some of its side effects on gastro-intestinal (GI) system (ulceration).[2]Topical NSAIDS when used as patch, gels, creams or sprays; penetrate the skin, subcutaneous tissue, fat and muscle in amounts that are sufficient to exert a therapeutic effect in the absence of high plasma concentrations.[3]

Data indicate that topical NSAIDs are effective at relieving pain in a number of acute and chronic pain indications like in treatment of acute post-operative pain, ankle sprain[4] and chronic arthritis. In patients with non-articular rheumatism and traumatic painful soft tissue injuries, it was shown that the topical ketoprofen patch was significantly more effective than placebo at reducing pain during daily activities and spontaneous pain after 7 days treatment. Pharmacokinetic data indicates that although plasma levels of ketoprofen are higher when the drug is administered as a patch versus a gel, the total systemic bioavailability of ketoprofen 100 mg administered via a patch is no greater than 10 % of that reported for ketoprofen 100 mg administered orally. The drug remains continually present in the tissue subjacent to the site of application because the patch facilitates ketoprofen delivery over a 24-hour period.[3] Fentanyl is a phenylpiperidine-derivative synthetic opioid agonist. It acts predominantly on the μ-opiate receptor.

As an analgesic, it is 75 - 125 times more potent than morphine. Transdermal fentanyl preparations 25 mcg to 100 mcg per hour results in peak plasma fentanyl concentration in about 18 hours that tends to remain stable during the presence of the patch, followed by a decreasing plasma concentration for several hours after removal of the delivery system.

These transdermal patches contain a depot of fentanyl that provides adequate drug to produce stable fentanyl concentrations for 3 consecutive days. Transdermal patch applied before the induction of anaesthesia and left in place for 24 hours decreases the amount of parenteral opioid required for post-operative analgesia.[5]

This study was undertaken to determine the effects of transdermal patches of ketoprofen and fentanyl in respect to post-operative pain relief, duration of analgesia, side effects and patient satisfaction.

METHODS

This was a prospective, single (patient) blinded, simple randomized, comparative study carried out in the Department of Anaesthesia of a 500+ bedded tertiary care teaching hospital in North Eastern India, after receiving ethical approval from the Institutional Ethical Committee. The duration of the study was 6 months (April 2021 to September 2021). 60 patients who satisfied the inclusion criteria were included in the study after taking their informed written consent. Prior to the study, it was determined that if any patient in any of the groups dropped out during the study, that patient would be replaced by another patient, of more or less similar demographic profile, who would meet the inclusion criteria till 30 patients in each group was reached. No patient dropped out during the entire study.

Inclusion Criteria

1. Patients undergoing major abdominal surgeries under general anaesthesia who gave informed written consent for participating in the study.
2. Patients aged 18 - 60 years of either sex.
3. ASA physical status I or II.

Exclusion Criteria

1. Patients undergoing emergency surgeries.
2. Pregnant and lactating women.
3. History of allergy to drugs, transdermal patches (if any).
4. Any history of opioid abuse/prolonged opioid therapy/opioid tolerant prior to the study.
5. Any prior history of asthma, skin diseases.
6. Any kidney or liver disease.
7. Patients having any form of pre-existing cardiac arrhythmias, bradycardia, uncontrolled hyper-tension, diabetes mellitus, neurological diseases.
8. Patients on anti-coagulants or having any haematological abnormalities.

Thorough pre-anaesthetic check-ups were performed on the selected patients a day before the surgery and instruction on fasting for at least 8 hours before the surgery was given. The sixty patients included in the study were divided into two groups by simple randomization. Group K (30 patients)

received ketoprofen 100 mg transdermal patch 4 hours before surgery and Group F (30 patients) received fentanyl (25 mcg/hour) transdermal patch 4 hours before surgery. The patches were applied on a dry, non-irritated, non-hairy area of the skin either over left shoulder region or on upper back after cleaning the area with spirit swab. Patients were monitored closely after application of patches. In patients of Group K (ketoprofen group), the ketoprofen transdermal patch (100 mg) was replaced after 24 hours of initial application as per the instruction from the manufacturer of the drug. All patients were pre-medicated with injection pantoprazole 40 mg, injection palonosetron 0.075 mg, injection glycopyrrolate 200 mcg and injection fentanyl 2 mcg/kg prior to surgery. General anaesthesia was induced using injection propofol. Intubation was facilitated using injection succinylcholine. Non-depolarising muscle relaxant – injection atracurium besylate was used intra-operatively for muscle relaxation. Inhalational anaesthetic sevoflurane was used along with nitrous: oxygen (66 % : 33 %). Intra-operatively, after intubation, infusion paracetamol 1000 gm was administered i.v. in patients of both the groups. After surgery, residual effect of atracurium besylate was antagonised using neostigmine+ glycopyrrolate.

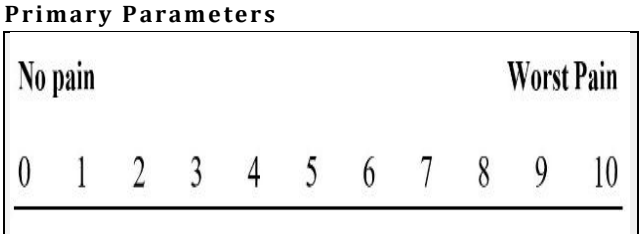
After spontaneous effort of respiration returned, patients were extubated following proper oral and oropharyngeal suctioning. In both the groups, reversal time was comparable; no patient in either group took more than five minutes for complete reversal. After reversal from general anaesthesia, patients were subsequently sent to post anaesthesia care unit (PACU) for observation and evaluation of the effects of the drugs under study. Pain was assessed post-operatively every 4 hours up to 24 hours post-surgery using VAS and VRS.

Sedation was also assessed using Ramsay sedation scale at same intervals. All resuscitative measures were kept in hand including mechanical ventilator in the PACU to manage any untoward circumstances during the stay of the study subjects. Infusion paracetamol 1000 gram was kept in hand for rescue analgesia. In Group K patients, the ketoprofen transdermal patch (100 mg) was replaced after 24 hours of first application as per the instruction from the manufacturer of the drug. Pain was assessed for the first 24 hours after surgery after which the transdermal patches were withdrawn in both the groups. The patients were kept on the second day (24 hours) in PACU for observation and thereafter shifted to ward/discharged as per the decision from the surgery team.

Patients were assessed clinically in respect to efficacy with safety parameter of the drugs under study. Clinical assessment was done post-operatively at 4, 8, 12, 16, 20, 24, hour time interval after application of patch.

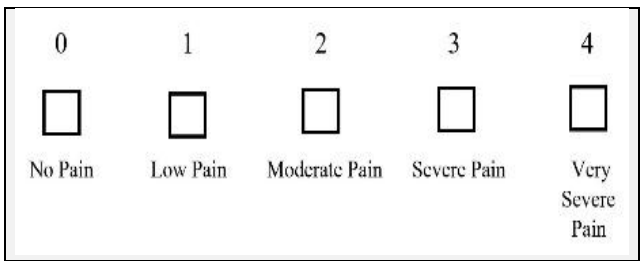
The patients were assessed for drug response by the following parameters.

Primary Parameters



Visual Analogue Scale (VAS)[6]

Where 0 (zero) is no pain and 10 (ten) is worst imaginable pain. Patients were explained about this method of pain scoring on the pre-operative visit and they were asked to mark on the line which represented their level of perceived pain severity and the scale was scored by measuring the distance from the no pain end to the point marked by the patient, measured in centimetres with a standard scale. Infusion paracetamol 1000 mg i.v. was given as rescue analgesic whenever the pain score was ≥ 4 or if the patients demanded so.



Verbal Rating Scale (VRS)[7]

Where 0 (zero) is no pain and 4 (four) is very severe pain. Infusion paracetamol 1000 mg i.v. was given as rescue analgesic whenever the pain score was > 2 or if the patients demanded so.

Secondary Parameters

1. Ramsay sedation scale[8]
2. Use of infusion paracetamol 1000 mg i.v. as rescue analgesic.
3. Patient satisfaction score (Likert Scale)
4. Anxiety score (State-Trait Anxiety Inventory – STAI)

Blood pressure (BP), heart rate (HR), oxygen saturation (SpO_2) and electrocardiogram (ECG) were continuously monitored for 48 hours post-surgery in PACU. Local side effects like itching, redness, swelling and systemic side effects like constipation, hematemesis, headache, dizziness, nausea, vomiting, and generalised weakness were noted and treated accordingly. Sedation was assessed using Ramsay sedation scale. Scores more than 3 were considered as sedation.

1. Anxious and agitated or restless
2. Co-operative, oriented and tranquil
3. Responds to command only
4. Brisk response to light glabellar tap or loud auditory stimulus
5. Sluggish response to light glabellar tap or loud auditory stimulus
6. No response can be elicited

Ramsay Sedation Scale[8]

Statistical Analysis

The data were expressed as mean ± SD unless specified otherwise. Analysis of efficacy was done using VAS and VRS scores of the two groups. Student's t-test was used to compare the mean VAS and VRS respectively of the two groups. P value < 0.05 was considered as statistically significant. The data entry and all statistical analysis were done using Statistical Package for Social Sciences (SPSS) for Windows (version 20.0 Chicago, SPSS Inc.) and Microsoft Excel 2019.

RESULTS

The demographic characteristics of the patients in the two study groups were comparable as shown in Table 1. The average age in Group K was 37.5 ± 12.33 and in Group F was 36.37 ± 14.37. The average weight in Group K was 65.2 ± 9.59 and in Group F was 64.9 ± 10.38. The mean duration of surgery of group K was 131.5 ± 20.2 minutes and Group D was 134.9 ± 22.6 minutes.

Demographic Variable	Group K Mean ± SD	Group F Mean ± SD	P Value
Age (years)	37.5 ± 12.33	36.37 ± 14.37	0.745
Weight (kg)	65.2 ± 9.59	64.9 ± 10.38	0.908
Surgery duration (minutes)	131.5 ± 20.2	134.9 ± 22.6	0.540

Table 1. Demographic Profile

(Student's t test was used to calculate p value)

Pain was assessed post-operatively using VAS and VRS score in the two groups. In Group K, mean VAS score at 4, 8, 12, 16, 20 and 24 hour time interval post-operatively were 1.83 ± 0.37, 2.33 ± 0.47, 2.73 ± 0.44, 3.00 ± 0.45, 2.76 ± 0.42 and 2.60 ± 0.48 respectively. In Group F, mean VAS score at 4, 8, 12, 16, 20 and 24 hour time interval post-operatively were 1.70 ± 0.58, 2.2 ± 0.54, 1.53 ± 0.49, 1.23 ± 0.80, 1.30 ± 0.59, 1.36 ± 0.66 respectively.

Time Interval Post-Operatively (in Hours)	VAS Score Group K (Mean ± SD)	Group F (Mean ± SD)	P Value
4	1.83 ± 0.37	1.70 ± 0.58	0.305
8	2.33 ± 0.47	2.2 ± 0.54	0.324
12	2.73 ± 0.44	1.53 ± 0.49	< 0.0001
16	3.00 ± 0.45	1.23 ± 0.80	< 0.0001
20	2.76 ± 0.42	1.30 ± 0.59	< 0.0001
24	2.60 ± 0.48	1.36 ± 0.66	< 0.0001

Table 2. Intergroup Comparison of Mean VAS of Group K and Group F

(Student's t test was used to calculate p value)

The differences in VAS scores were comparable at 4 hour and 8 hour time interval post-operatively ($p > 0.05$). Thereafter, at 12, 16, 20, 24 hour time interval post-surgery, the difference in mean VAS was found to be statistically highly significant ($p < 0.0001$).

The peak analgesic effect was seen in case of ketoprofen group at 4 hours post operatively (approximately 10 hours after application of ketoprofen patch) and of fentanyl group during and after 12 hours post operatively (18 hours after application of fentanyl patch).

In group K, the mean VRS scores at 4, 8, 12, 16, 20 and 24 hour time interval post-operatively were 0.93 ± 0.51, 1.10 ± 0.54, 1.16 ± 0.37, 1.43 ± 0.67, 1.30 ± 0.46 and 1.13 ± 0.56 respectively. In group F, the mean VRS scores at 4, 6, 12, 16, 20 and 24 hour time interval were 0.73 ± 0.57, 1.00 ± 0.45, 0.70 ± 0.45, 0.53 ± 0.49, 0.63 ± 0.48 and 0.67 ± 0.47 respectively.

Time Interval Post-Operatively (in Hours)	VRS Score Group K (Mean ± SD)	Group F (Mean ± SD)	P Value
4	0.93 ± 0.51	0.73 ± 0.57	0.157
8	1.10 ± 0.54	1.00 ± 0.45	0.439
12	1.16 ± 0.37	0.70 ± 0.45	0.0001
16	1.43 ± 0.67	0.53 ± 0.49	< 0.0001
20	1.30 ± 0.46	0.63 ± 0.48	< 0.0001
24	1.13 ± 0.56	0.67 ± 0.47	0.0011

Table 3. Intergroup Comparison of Mean VRS of Group K and Group F

(Student's t test was used to calculate p value)

The differences in mean VRS scores were comparable at 4 hour and 8 hour time interval post-surgery ($p > 0.05$). Thereafter, at 12, 16, 20, 24 hour time interval post-surgery, the difference in mean VRS was found to be statistically significant ($p < 0.05$).

Time Interval Post-Operatively (in Hours)	Ramsay Sedation Scale Score Group K (Mean ± SD)	Group F (Mean ± SD)	P Value
4	2.43 ± 0.49	2.56 ± 0.49	0.308
8	2.30 ± 0.64	2.53 ± 0.67	0.179
12	2.40 ± 0.49	2.67 ± 0.65	0.074
16	2.50 ± 0.56	2.77 ± 0.42	0.039
20	2.16 ± 0.58	2.63 ± 0.48	0.001
24	2.43 ± 0.59	2.73 ± 0.44	0.029

Table 4. Ramsay Sedation Scale Scores

(Student's t test was used to calculate p value)

Difference in mean Ramsay sedation scale score in the two groups was comparable during 4 hour, 8 hour and 12 hour post-surgery time interval. From 16 hours till 24 hours time interval post-operatively, the differences were statistically significant but clinically not significant. In group F, the highest score in Ramsay sedation scale was 3.

2 patients during 16 hour post-surgery time interval and 1 patient during 20 hours post-surgery time interval needed rescue analgesic in Group K. No patient in group F required any rescue analgesic during the study period. The patient satisfaction score and anxiety score were comparable in the two groups all throughout the study period. Majority of the patients in both the groups were satisfied with the transdermal patch therapy and expressed it as GOOD (95 %).

The systolic, diastolic blood pressure, heart rate and SpO_2 were stable all throughout the study period and 24 hours after removal of patch in both the groups. There was no statistically significant difference present in the mean haemodynamic parameters of the two groups.

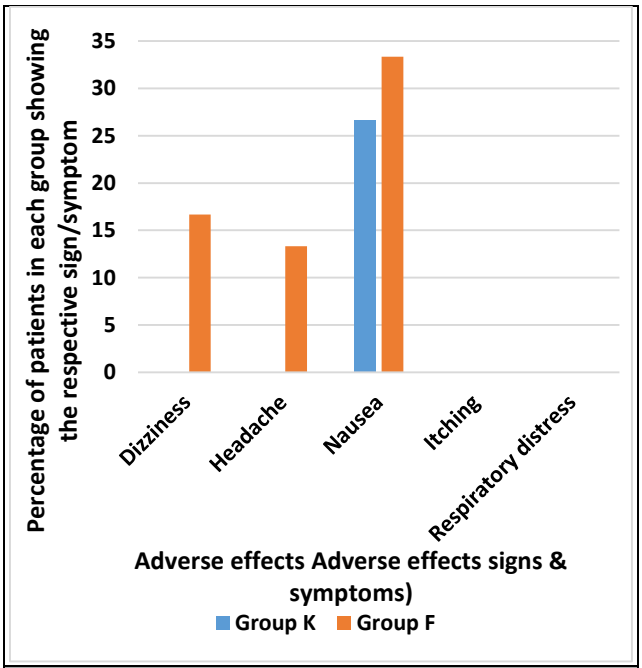


Figure 1. Adverse Effects in Percentage (%)

There was no serious systemic adverse effect observed in both the groups. In group K, 26.67 % patients had nausea which was treated symptomatically. In Group F, 16.67 %, 13.33 % and 33.33 % patients complained of dizziness,

headache and nausea which were relieved symptomatically. No patient showed any sign of respiratory distress. Average time of return of intestinal peristalsis post-surgery in patients of both the groups was comparable. No patient complained of any itching, pruritis or any erythema was observed at the site of patch application.

DISCUSSION

Patients undergoing major abdominal surgery suffer a lot from pain in the first day or two post-operatively due to extensive tissue trauma. The post-operative pain is managed by giving drugs through different routes. But the goal should be to provide maximum relief of pain with minimum side effects and improved patient compliance. Transdermal route of drug delivery is advantageous because it provides sustained release of drug, uniform plasma levels, improved bioavailability, reduced adverse effects, patient compliant and easy to withdraw the drug by simply removing the patch. Skledar et al.[9] had said fentanyl iontophoretic transdermal system (ITS) had shown high patient satisfaction rates, and was described by patients and investigators as easy and convenient to use. They said in the present health care environment, additional data is required to establish the cost-benefit ratio of this technology in optimizing patient's recovery from surgery. In our study, we have compared the efficacy of two groups of analgesic drugs - NSAID (ketoprofen) and opioid (fentanyl) given via transdermal drug delivery system. The average weight, age and duration of surgery were comparable in both the groups in our study. Both mean VAS and VRS scores of the two groups were comparable during 4 hour and 8 hour post-operatively. During 12 hour, 16 hour, 20 hour, and 24 hour, the differences in mean VAS and VRS scores of the two groups were statistically significant ($p < 0.05$).

Caplan et al.[10] in their clinical trial on transdermal fentanyl for post-operative pain management, applied fentanyl patches (just before the surgery) which delivered 75 mcg/hr on healthy adult patients who underwent major shoulder surgery. They found patients in their active group required significantly less morphine than placebo group during the 24-hour period that systems were in place and the first 12 hours after removal. They also found that the respiratory rate in the active group was lower than in the placebo group during the 13- to 24-hour time interval of their system application. In our study, we used fentanyl transdermal patches (applied 4 hours prior to the surgery) that delivered fentanyl 25 mcg/hr. we did not observe any sign of respiratory depression in our fentanyl group during the time the patches were in place or in the first 24 hours after patch removal. Caplan et al.[10] found the incidence of vomiting was more frequent in the active group (73 %) whereas in our study the incidence of nausea in fentanyl group was 33.3 %. Sandler et al.[11] in their double blind, placebo controlled trial on transdermal fentanyl (50 mcg/hr and 75 mcg/hr) after abdominal hysterectomy found that application of transdermal fentanyl 2 hours pre-operatively was associated with moderate supplementary opioid requirements for analgesia in the early post-operative period and ongoing opioid supplementation for at least 72 hours. They found good analgesia with their combination therapy but it was associated with high incidence of respiratory depression which required intensive monitoring, O_2 supplementation, removal of the patches in approximately 11 % of the patients and opioid reversal with naloxone in approximately 8 % of the patients. In our study, the use of fentanyl transdermal drug delivery system (TDS) 25 mcg/hr provided satisfactory analgesia post-operatively without any severe adverse effect like respiratory depression. Though, we kept injection paracetamol 1 gm to be given via infusion for rescue analgesia, no patient in our group F complained of any breakthrough pain and therefore rescue analgesia wasn't required in group F. In our group K, three patients needed rescue analgesia and were treated using paracetamol infusion.

Fentanyl TDS was developed to produce stable, long term fentanyl plasma concentrations in effort to provide adequate sustained analgesia for chronic, cancer related pain. With regard to post-operative analgesia, ketoprofen transdermal patch has been compared by some authors with diclofenac transdermal patch[12] and buprenorphine transdermal patch[13] in patients who underwent major abdominal or orthopaedic surgery. But there are only few studies that too encompassing only mandibular third molar surgery to determine the efficacy and side effects of ketoprofen and fentanyl for post-operative analgesia. Fentanyl transdermal patches (75 mcg/hr, 50 mcg/hr) have mainly been employed and studied in relation to treating breakthrough cancer related pain in patients who require long term narcotic pain relief therapy.

CONCLUSIONS

Fentanyl transdermal patch (25 mcg/hr) applied 4 hours prior to surgery, had an edge over ketoprofen transdermal patch (100 mg) in attenuating post-operative pain in otherwise healthy adult patients who underwent major abdominal surgeries under general anaesthesia (GA). Fentanyl TDS showed longer duration of action than ketoprofen TDS without showing any serious side effects like respiratory depression, drowsiness, haemodynamic instability or delayed return of intestinal peristalsis post abdominal surgery. Mild side effects observed in few patients like nausea, headache, dizziness in the fentanyl group and nausea in the ketorolac group were treated symptomatically.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jemds.com.

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