Original Article

Early post-operative relief of pain and shivering using diclofenac suppository versus intravenous pethidine in spinal anesthesia

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Abstract

Background: Pain and shivering are two challenging components in the post operative period. Many drugs were used for prevention and treatment of them. The aim of this study was to compare the effects of prophylactic prescription of diclofenac suppository versus intravenous (IV) pethidine in spinal anesthesia.

Materials and Methods: We conducted a multi central, prospective, double-blind, randomized clinical trial on a total of 180 patients who were scheduled for surgery under spinal anesthesia including 60 patients in three groups. Patients were randomly allocated to receive 100 mg sodium diclofenac suppository or 30 mg IV pethidine or placebo. Categorical and continuous variables were analyzed by Chi-square test, *t*-test, Mann-Whitney and ANOVA or Kruskal-Wallis tests.

Results: There was no statistical difference with regard to patient characteristics and hemodynamic indices among the three groups. Nine (15%), 10 (16.65%) and 24 (40%) of patients in diclofenac, pethidine and control groups reported pain and 2, 2, 7 patients received treatment due to it, respectively ($P = 0.01$). Prevalence of shivering in pethidine group and diclofenac group was the same and both of them were different from the control group ($P < 0.001$). Pruritus was repetitive in the pethidine group and was statistically significant ($P = 0.036$) but, post-operative nausea and vomiting was not significantly different among groups.

Conclusion: A single dose of sodium diclofenac suppository can provide satisfactory analgesia immediately after surgery and decrease shivering without remarkable complications. This investigation highlights the role of pre-operative administration of a single dose of rectal diclofenac as a sole analgesic for early post-operative period.

Key words: Pethidine, post-operative pain, shivering, suppository diclofenac

Introduction

Spinal anesthesia is the most consistent block for lower abdomen and orthopedic surgery[1] and shivering is its common complication.[2] It is usually defined as readily detectable fasciculation or tremor of the face, jaw, head, trunk or extremities lasting longer than 15 s. Post-operative pain is another important impediment of recovery time. Therefore, reducing the pain after surgery is important.[3]

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Prevention of post-operative pain and post-anesthetic shivering, should be considered and managed as two important components to improve the outcome in terms of remarkable consequences such as reduced oxygen consumption and CO_2 production, catecholamine release, cardiac morbidity, intracranial pressure, intraocular pressure, blood loss and improved wound healing.[4]

A wide range of drugs, including pethidine, buprenorphine, clonidine and non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to be effective in suppressing shivering or relieving pain. Meperidine hydrochloride also known as pethidine is a synthetic opiate agonist belonging to the phenylpiperidine class. Pethidine, in particular, is remarkably effective in post-operative shivering and pain treatment when given intravenously (IV). It stops shivering and pain in the majority of adults.[5] Pethidine has various side-effects such as hypotension, nausea, vomiting, decreased gastrointestinal (GI) motility, itching, respiratory depression, tachycardia and physical dependency.[6,7]

Sodium diclofenac (NSAIDs category) has been shown to have analgesic affects in different conditions. It has a wide

indication in post-operative pain relief[8,9] through a direct anti-inflammatory and analgesic effect and indirect effect on chemical mediators responsible for painful impulses. Moreover, Sodium diclofenac neither causes respiratory depression, nor other side-effects such as vomiting, itching and hemodynamic instability. Sodium diclofenac like other NSAIDs has some GI effects and there is a theoretical risk of post-operative hemorrhage as it prolongs bleeding time and reduces platelet aggregation.

Many studies have been conducted to compare NSAIDs with opioids in the post-operative period, but there have been few studies to determine the efficacy of diclofenac suppository and pethidine. The aim of the present study was to compare sodium diclofenac and pethidine with regards to the prevention of shivering, post-operative pain management and their adverse reactions versus the control group, after spinal anesthesia.

Materials and Methods

After ethic committee approval, 180 patients with American Society of Anesthesiologist class I-II (ASA class), aged 18-65 years old, scheduled for spinal anesthesia during lower abdomen or orthopedic surgery, were included in this multi central, prospective, randomized, clinical trial from 2009-2010. The duration of surgeries was around 60 min which needed a maximum block level of T4 and minimum block levels of T_{10}. Written informed consent was obtained from each patient pre-operatively.

Patients with a history of malignancy, epilepsy, hematological disorders, hepatic or renal insufficiency, peptic ulcer or active GI bleeding, chronic pain, long-term steroid therapy or continuous usage of analgesic drugs, relevant drug allergies or asthma, uncontrolled hypertension, neurologic or psychological disorders, alcohol abuse, opium addict or using any drug that modifies pain perception and inability to tolerate rectal sodium diclofenac were excluded from the study.

After IV line preparation, a 5-7 mL/kg lactated ringers solution was infused to all patients. Patients received no premedication and upon arrival of patients into the operating room, electrocardiogram, peripheral oxygen saturation (SPO_2), noninvasive blood pressure (BP), respiratory rate (RR) and peripheral temperature (T) were monitored and recorded every 5 min until the end of surgery and vital signs were recorded every 15 min in the Post Anesthesia Care Unit for 30 min and every 60 min in the wards up to 3 h. All preloading fluids and IV infusions used during operations were pre-warmed to a temperature of approximately 37°C. Operating room temperature was kept at 22 ± 1°C and a standard double-layered blanket was used to cover all patients.

Spinal anesthesia was performed on the sitting position at L_3-L_4 level through a midline approach using a 25 gauge Quincke spinal needle by 100 mg preservative free lidocaine 5% at a rate of 0.2 mL/s. After spinal anesthesia, patients were kept in the supine position and oxygen 5-6 L/min was given through a face mask.

Simple random sampling was carried out to randomly allocate patients in time duration based on patients refereeing. Patients were randomly allocated into three groups, Group I received 100 mg sodium diclofenac suppository, Group II received 30 mg IV pethidine (3 mL) and control group (Group III) received 3 mL preservative free normal saline as placebo. Diclofenac was given immediately after spinal anesthesia and before starting the surgery. Pethidine and placebo was given at the similar time, after stabilizing level of anesthesia (appropriate dermatome level for the surgery) and starting the operation. Both the patients and the observer who recorded data were blinded to the group allocation.

Recording data was started from the time of drug injection into the intrathecal space as time zero. Duration of pain free period was measured from the end of the surgery up to patients' pain perception in the operated area. Hypotension, a 30% decrease in systolic BP from the baseline or systolic BP <100 mmHg and bradycardia and heart rate (HR) <50 beats/min was treated by IV ephedrine 5-10 mg plus crystalloid fluids; and IV atropine 0.5 mg respectively. Nausea and vomiting were also evaluated and treated with 0.15 mg/kg IV metoclopramide.

Shivering was categorized as inconsiderable shivering (no visible shivering with or without piloerection or peripheral vasoconstriction) and moderate/severe shivering (muscular activity in one or more than one group of muscles and/or whole body shivering).

The sensory block level was assessed using a pin prick test by a short bevel needle along the mid-axillaries line bilaterally. After four dermatome block regression or at the 30th min, pain assessment was done using the visual analogue pain scale (VAS) (0 = no pain, 10 = the most severe pain) and repeated every 1 h in post-operative wards. If the post-operative VAS was higher than 6 and/or patients felt pain in the surgery field and asked for analgesia or severe shaking chills, they were treated by 0.5 mg/kg pethidine (maximum dose 35 mg). In the recovery room, patients were evaluated every 5-15 min; and every 1-2 h in the post-operation wards. An Anesthesiologist assessed the pain score in each patient.

Adverse reactions like respiratory depression (RR lower than 8 breath/min), SPO_2 lower than 95% despite

supplementary O_2, urinary retention and pruritus was noted and recorded throughout the post-operative period. To facilitate the double-blinding method, the medication and suppository was prepared and prescribed after spinal anesthesia and patients were sedated by 1-2 mg IV midazolam by the nurses who were not involved in the study. Patients were visited at hospital discharge and asked about any complications.

The analyses were performed at the Statistic and Social Medicine Department. The main variable in this study was pain and the sample size was calculated on the basis of mean differences of pain perception (VAS score) in other studies. In the early evaluation, the mean difference in pain VAS score considered one unit (1.5 ± 0.5 from the statistical point of view) $\alpha = 0.05$ and power = 0.85 resulted in a minimum of 55 patients in each group so, 60 patients per study group were considered and scheduled. The power analysis showed that a total sample size of about 180 patients will be sufficient to detect a difference of one in VAS score between groups. For categorical variables (sex, nausea/vomiting) Chi-square test or Fisher's exact test was used. Mean of continuous data were compared between three groups using Mann-Whitney and ANOVA tests. All statistical analyses were performed using SPSS software (version 11.5, Chicago, IL, USA). The values are expressed as mean ± standard deviation and the significance level was defined as a $P < 0.05$.

Results

All patients ($n = 180$) completed the study; there was no statistical difference in patients' demographic data [Table 1].

There was no statistical difference between HR of three groups in time zero ($P = 0.291$) and 30 min ($P = 0.133$). There had been reported a decrease in HR from base line to 60th min, after that an increase in HR at 120 and 180 min was recorded. The rise in HR was significantly higher in Group III (control group) and the difference between Group I-III ($P = 0.038$) and II-III ($P = 0.025$) was significant, too.

After spinal anesthesia and prophylactic prescription of suppository sodium diclofenac, pethidine and placebo to the patients, we found a significant decrease in BP in all groups and minimum BP was detected between 30 and 60 min. BP started to rise together with HR in all groups. Group I and II had no significant difference ($P = 0.097$), but the difference was significant between Groups I-III ($P = 0.024$) and II-III ($P = 0.037$) [Tables 2-4].

In Groups I and II, shivering was significantly lower than the control group but there was no difference between Groups I and II ($P = 0.570$). $P < 0.001$ between Groups I-III and II-III.

In Group I, nine (15%) patients reported pain and two of them were treated. In Group II, 10 patients (16.6%) reported pain and two received medication and in Group III 24 (40%)

Table 1: Demographic characteristics of three groups

Parameters	Group I	Group II	Group III	*P* value
Age (years)	37.84 (±14.36)	39.95 (±17.19)	38.33 (±15.56)	0.14
Sex (female/male)	20/40	21/39	18/42	0.37
ASA I/II	50/10	48/12	53/7	0.26
BMI (kg/m^2)	22.31 (±5.6)	23.27 (±5.9)	22.58 (±5.2)	0.21

Data are represented as mean±SD, demographic data included 60 patients each group, there was no significant statistical difference between groups, SD = Standard deviation, ASA = American Society of Anesthesiologists, BMI = Body mass index

Table 2: The heart rates (beats/minutes) fluctuation in three groups of patient from zero time up to 180 min

Time sections	Group I (*n* = 60)	Group II (*n* = 60)	Group III (*n* = 60)	*P* value
0 min	74.85±13.66	77.00±12.39	76.00±11.09	0.091*
30 min	73.66±9.42	71.50±9.62	75.16±10.86	0.133*
60 min	69.13±10.05	69.05±11.43	75.18±12.43	0.004†
120 min	70.88±12.46	72.45±12.82	76.06±14.06	0.008†
180 min	75.75±9.87	72.81±8.67	77.38±10.76	0.038†

*Data are presented as mean±SD, *P value between groups I and II, †P value between groups I and III, SD = Standard deviation*

Table 3: Systolic blood pressure (mmHg) at different intervals (mean ± SD)

Time sections	Systolic BP (mmHg)		
	Group I (*n* = 60)	Group II (*n* = 60)	Group III (*n* = 60)
0 min	127.85±13.08	121.35±14.93	131.50±16.28
30 min	107.91±11.99	109.93±13.16	114.80±11.49
60 min	109.65±11.38	113.10±11.13	118.75±9.62
120 min	113.50±11.18	115.38±12.50	121.03±13.56
180 min	113.70±10.26	115.91±11.87	120.26±10.70
P value*	<0.05		

*Data are presented as mean±SD, BP = Blood pressure, SD = Standard deviation, *P value between groups I and II, I and III, and II and III*

Table 4: Diastolic BP (mmHg) at different intervals

Time Sections	Diastolic BP (mmHg)			*P* value*
	Group I (*n* = 60)	Group II (*n* = 60)	Group III (*n* = 60)	
0 min	80.41±8.80	78.43±9.26	81.0±8.98	0.026
30 min	71.93±8.23	73.03±8.12	73.51±7.74	0.049
60 min	72.96±7.72	74.91±5.74	75.63±7.24	0.045
120 min	72.88±8.50	75.08±6.54	76.80±8.19	0.041
180 min	73.93±8.32	75.40±7.48	77.25±7.40	0.037
P value†	0.037			

*Data are presented as mean±SD, BP = Blood pressure, SD = Standard deviation, *P value between groups I and III, †P value between groups II and III*

patients had post-operative pain and seven asked for analgesics ($P = 0.01$) [Table 5].

Pain free period in Group I was 42.2 ± 12 min, in Group II was 38.3 ± 18 min and in Group III was 22.46 ± 21 min ($P = 0.038$).

In Table 6, the frequency of post-operative nausea and vomiting among three groups is shown.

Regarding other adverse reaction, there was no respiratory depression, excessive blood loss and urinary retention in our patients and the SPO_2 was in the normal range. Pruritus was repetitive in the pethidine group and was statistically significant compared with other groups (nine cases [15%] in pethidine group and no one in other groups; $P = 0.036$) and two of them needed treatment.

Discussion

Decisions on post-operative analgesia and relieving post spinal anesthesia shivering should be based on the evidence of efficacy and safety. Various opioid and non-opioid agents have been used to prevent, control and treat post-operative pain and shivering but they are not free from side effects.[5,10]

Pethidine is known as a standard regimen for post anesthesia shivering suppression and pain management.[10] Due to the wide range of side effects of pethidine, replacement with other analgesics has always been considered.

Post spinal shivering affects about 30-50% of patients.[1] Our results showed that the frequency of shivering was six (10%) in pethidine group and 38.33% in the control group. This finding corroborates with the finding of Piper *et al.*, who reported that incidence of post-operative shivering was 16.6% in pethidine pre-treatment group.[10]

Our study reports comparable incidence of shivering when using sodium diclofenac suppository or pethidine intravenously, so sodium diclofenac could be prescribed instead of pethidine as prophylaxis for shivering.

Based on our finding, analgesic effect of 100 mg rectal diclofenac before the surgery was the same as 0.5 mg/kg IV pethidine as patients showed similar VAS score in 60th min after surgery and it was lower than control group.

Rashid and Jaruidi[9] evaluated the efficacy of 100 mg rectal diclofenac for analgesia after the surgery. Their results revealed that VAS was significantly less in the study group compared with the control group who did not receive any drug.[9] In a study assessing the efficacy of diclofenac on patient outcomes after cardiac surgery, concluded that sodium diclofenac has a significant opioid-sparing effect after coronary artery bypass graft.[11]

Diclofenac sodium given alongwith premedication prior to spinal surgery has been reported to significantly decrease the frequency of persistent postoperative pain, in comparison to patients treated with pethidine.[12]

Prescription of pre-operative rectal diclofenac for post-operative analgesia indicates that it considerably delays the onset of post-operative pain and is adequate as a sole analgesic for early post-operative period.[13] These findings are in consonance to the results of our study, wherein the .preemptive analgesic effect of diclofenac was comparable to pethidine. Because of a theoretical risk of post-operative hemorrhage with diclofenac as it prolongs the bleeding time and reduces platelet aggregation, there is a reluctance among surgeons to use diclofenac. A study showed pre-operative rectal diclofenac is associated with increased intraoperative blood loss.[14] However, in our study no extra intraoperative bleeding was observed requiring active treatment; besides, in contrast to Legeby's study[15] we had no excessive post-operative blood loss compared to control group. Intraoperative and post-operative hemodynamic state was stable in all groups.

There are some reports about local and GI side-effect of NSAIDs rectal suppositories including ischemic colitis, proctitis, rectal bleeding, abdominal pain, local allergic reactions, itching and swelling, however these are rare case reports,[16-20] and moreover our patients did not have any complaint in relation with rectal route of diclofenac prescription, local or systemic side-effects of suppository

Table 5: Frequency and severity of pain in 60th to 120th min after spinal anesthesia among three groups

Pain category	Group I ($n = 60$) (%)	Group II ($n = 60$) (%)	Group III ($n = 60$) (%)
Mild pain (VAS 0-III)	51 (85)	50 (83.4)	36 (60)
Moderate pain (VAS IV-VI)	7 (11.7)	8 (12.3)	17 (28.3)
Severe pain (VAS VII-X)	2 (3.3)	2 (3.3)	7 (11.7)
P value (ANOVA)*	0.01		

**P value between groups I and I, II and groups II and III, ANOVA = Analysis of variance, VAS = Visual analogue pain scale*

Table 6: Frequency of nausea and vomiting among three groups

Complications	Group I ($n = 60$) (%)	Group II ($n = 60$) (%)	Group III ($n = 60$) (%)
Nausea	7 (11.7)	7 (11.7)	8 (13.8)
Vomiting	3 (5)	2 (3.3)	2 (3.3)
P value	0.36		

Data are represented as number and percent

diclofenac, similar to study of Hedayati *et al.*,[21] which can be ascribed to our tight exclusion criteria.

Hemodynamic instability, Respiratory depression, pruritus, nausea and vomiting are the most common complication after prescription of pethidine.[7] In our study, pre-treatment with a single dose of pethidine or suppository of sodium diclofenac did not increase incidence of nausea and vomiting compared to control group.

Previous studies demonstrated pruritus as an important adverse reaction with pethidine prescription.[14] Our study emphasized this issue as the pruritus was frequent and considerable in pethidine group compared to diclofenac and control groups.

We found out that sodium diclofenac can provide satisfactory analgesia immediately after surgery and also decreases post spinal shivering. Although both sodium diclofenac suppository and pethidine effectively prevented shivering and pain after spinal anesthesia with an acceptable hemodynamic stability, low-cost and easy accessibility make NSAID's a valuable alternative for pethidine. Hence this study highlights the role of pre-operative administration of single dose of rectal diclofenac as a sole analgesic.

Future trials should possibly compare multiple repeated doses of sodium diclofenac suppository over a longer observation period probably spanning several days.

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