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Research article

Dexmedetomidine versus Nalbuphine for treatment of postspinal shivering in patients undergoing vaginal hysterectomy: A randomized, double blind, controlled study

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ABSTRACT

Objectives: Shivering is very distressing for the patient therefore, control of postspinal shivering is essential for proper perioperative care. This study was designed to compare the efficacy, safety and cost effectiveness of Dexmedetomidine and Nalbuphine in the treatment of postspinal shivering.
Methods: In this prospective, randomized, double-blind, placebo controlled study, 75 American Society of Anesthesiologists Grade I and II females scheduled for vaginal hysterectomy under spinal anesthesia, who developed shivering grade 3 or 4 were included. The patients were randomized into three groups of 25 patients each to receive either Nalbuphine 0.07 mg/kg (group N) or Dexmedetomidine 0.5 μg/kg (group D) or saline (group C) as a slow intravenous bolus for treatment of shivering. Onset of shivering, grade of shivering, time for cessation, response rate, recurrence, hemodynamic parameters and adverse effects were observed at scheduled intervals.
Results: It was observed that the mean response time for control of shivering was significantly less in Group D (1.97 ± 0.61 min) compared to Group N (3.56 ± 0.82 min) and Group C (12.4 ± 3.74 min). Success rate in Group D was 100% compared to 92% in Group N and 32% in Group C. Relapse of shivering was observed more in patients of Group N (8.7%) as compared to Group D (0%) while shivering reappeared in 75% of patients who responded to saline treatment. Among the side effects, sedation was found in both groups N and D. Bradycardia and hypotension were more frequent in Dexmedetomidine group although none of the patients required treatment. Pain during injection was an outstanding complaint in Nalbuphine group.
Conclusion: Both Nalbuphine and Dexmedetomidine control shivering effectively, but Dexmedetomidine seems to be a better choice than Nalbuphine for treatment of postspinal shivering due to its shorter response time, lower recurrence rate and associated sedation. Meanwhile, Nalbuphine offers more hemodynamic stability and lower costs.

1. Introduction

Shivering is a relatively common problem encountered during the perioperative period. It is reported in 40–70% of patients undergoing surgery under regional anesthesia [1].

Along with nausea and vomiting, postanesthesia shivering is one of the leading causes of discomfort for patients. Shivering not only adds psychological stress to the patient but also physiologically leads to an increase in O_2 consumption by 200–500%, and increased carbon dioxide production which may lead to problems in patients with existing intrapulmonary shunts, fixed cardiac output, or limited respiratory reserve [1].

The primary cause of postanasthesia shivering is perioperative hypothermia. However, shivering associated with cutaneous vasodilatation (non-thermoregulatory shivering) also occurs [2]. As shivering has been reported in normothermic patients, other mechanisms such as inhibited spinal reflexes, apprehension, decreased sympathetic activity, pyrogen release, adrenal gland suppression, and respiratory alkalosis have been suggested [3].

Kranke et al. [4] extrapolated data from a meta-analysis regarding medications and dosing practices and concluded that prophylaxis against perioperative shivering is not cost effective, and that treatment strategies should start with external warming and then progress to pharmacologic interventions.

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Perioperative skin surface rewarming is a rapid way of obtaining the threshold shivering temperature while raising the skin temperature and improving the comfort of the patient. However, it is less efficient than pharmacological agents as skin temperature only contributes 20% to control of vasoconstriction and shivering [5].

Meperidine is probably the most efficient antishivering drug used. It is the only drug that decreases the shivering twice as much as the vasoconstriction threshold [$-6.1\ ^{\circ}C\ \mu g^{-1}$ ml *vs* $-3.3\ ^{\circ}C\ \mu g^{-1}$ ml with a slope ratio of 1.85] [6].

It has been postulated that meperidine's special anti-shivering effect is mediated by its κ-receptor activity [7]. Nalbuphine is a semisynthetic, mixed agonist antagonist opioid that has the characteristics of μ-antagonist and κ-agonist activities. It has a high affinity for κ-opioid receptors in the central nervous system [8]. A clinically important contribution of κ receptors is supported by the observation that meperidine reduces the intensity of cold-induced shivering even in the presence of moderate doses of naloxone, which presumably blocks μ receptors while having little effect on the relatively resistant κ receptors [9].

It was also postulated that the special antishivering effect of meperidine is mediated by its central α_2-activity [10]. Dexmedetomidine and meperidine are both central α_2-receptor agonists. Dexmedetomidine and meperidine additively reduced the shivering threshold in healthy adults by ≈2 °C, with only minimal sedation or respiratory toxicity [11]. Dexmedetomidine comparably reduces the vasoconstriction and shivering thresholds, thus suggesting that it acts on the central thermoregulatory system rather than preventing shivering peripherally [12]. It also acts by blocking α2 receptors at the locus ceruleus of the brainstem and spinal cord thus causing sedation and analgesia [13].

Due to undesired side effects and lack of availability of meperidine we chose to study Nalbuphine and Dexmedetomidine which are more readily available.

The *primary outcome* of this prospective double-blind, randomized, controlled study was to clinically compare the ability of either drug to effectively abolish postspinal shivering (time to cessation of shivering). *Secondary outcome* includes hemodynamic effects, complications, side effects and cost effectiveness of Dexmedetomidine compared with those of Nalbuphine for treatment of shivering in women undergoing hysterectomy under spinal anesthesia.

2. Patients and methods

After obtaining approval from our hospital's ethics committee, this prospective double-blind, randomized, controlled study was conducted at the department of Obstetrics and Gynecology, Faculty of Medicine, El- Minia University Hospital from December 2014 to June 2015. The study involved 75 consecutive ASA class I & II patients scheduled for elective vaginal hysterectomy with or without repair of cystocele and/or rectocele. All patients gave written informed consent.

Excluded from the study were patients with known hypersensitivity to Dexmedetomidine or Nalbuphine, known history of alcohol or substance abuse, hyperthyroidism, cardiovascular diseases, psychological disorder, severe diabetes, gross neurologic impairment, serum creatinine >1.3 mg/dl, ages <35 or >85 yr, preoperatively determined need for postoperative intensive care, any conditions which would preclude from conducting regional anesthesia, such as bleeding tendencies (due to either primary disease or the use of anticoagulant drugs), and a likelihood of conversion to an abdominal approach.

A 2-operator technique was employed to maintain blinding. The study solutions were prepared by an investigator who was not involved in patient handling. Patients who developed post–spinal shivering were randomly (sealed envelope technique) allocated to one of three groups Group C: received an intravenous (iv) bolus of 0.9% normal saline (10 ml) administered over 2 min. Group N: received an intravenous (iv) bolus of 0.07 mg/kg nalbuphine (Nalufin, Amoun, 20 mg/ml) administered over 2 min. Group D: received an iv bolus of 0.5 μg/kg Dexmedetomidine hydrochloride (Precedex, Hospira, vial 200 mcg/2 ml) administered over 2 min. All treatment drugs were diluted with 0.9% saline to a 10 ml volume.

The anesthesiologist conducting the case and recording the data was unaware of the preparation administered. After standard anesthesia monitors were applied, Lactated Ringer's solution (10 ml/kg) was infused. With the patient in the sitting position, the lumbar region was prepped with Betadine. A 25 gauge Quincke's needle was introduced at L3-4 interspace. After free flow of cerebrospinal fluid was confirmed, Bupivacaine 0.5% (15 mg) was injected intrathecally and blockade up to T9-10 dermatome was achieved. All operating theatres in which the operations were performed maintained constant humidity (70%) and an ambient temperature of around 21 °C to 23 °C. Oxygen was administered to all the patients at a rate of 3 L/min via nasal cannula. Intraoperatively, patients were covered with 2 layers of surgical drapes and a cotton blanket postoperative. No means of active re-warming were used. Intravenous fluids and anesthetic drugs were administered at room temperature.

Standard monitoring of pulse rate, noninvasive blood pressure (NIBP), oxygen saturation (SpO_2), body temperature (axillary) were recorded before the commencement of surgery and thereafter every 5 min from the baseline (i.e. subarachnoid block), for the first hour; and every 15 min, for the rest of the observation period.

Grading of shivering was done as per Wrench et al. [14] which is: Grade 0: No shivering. Grade 1: One or more of the following: Piloerection, peripheral vasoconstriction, peripheral cyanosis but without visible muscle activity. Grade 2: Visible muscle activity confined to one muscle group. Grade 3: Visible muscle activity in more than one muscle group. Grade 4: Gross muscle activity involving the whole body.

Patients who developed either grade 3 or 4 shivering were included in the study. The attending anesthetist recorded the time in minutes at which shivering started after spinal anesthesia (onset of shivering), severity of the shivering (grade), time to disappearance of shivering in minutes (response time) and success rate (shivering ceased after treatment within 15 min). Duration of surgery was noted, and duration of spinal anesthesia was recorded by assessing spontaneous recovery of sensory block using pin-prick method and observing spontaneous movements of limbs in the postoperative period. If the shivering did not subside by 15 min, the treatment was considered ineffective. Recurrence of shivering was also noticed until the patient left the operating theatre. Patients who did not respond or in whom recurrence of shivering occurred were treated with Meperidine 30 mg.

Side effects like nausea, vomiting, bradycardia (<50/min), hypotension (>20% of baseline), pain during injection and sedation score were recorded. Sedation score was assessed with a four-point scale as per Filos et al. [15] 1: Awake and alert. 2: Somnolent, but responsive to verbal stimuli. 3: Somnolent, arousable to physical stimuli. 4: Unarousable.

Bradycardia, hypotension and vomiting were treated with atropine, ephedrine and granisetron, respectively, in titrated doses when required.

3. Sample size calculation

Sample size calculation was done using the equation provided by Eng, 2003 [16]. The means of time taken for cessation of postspinal shivering after treatment with either Nalbuphine or

Dexmedetomidine was considered the primary end point of this study. For a difference between the means of both drugs to be of value we hypothesized 180 s and a standard deviation of 180 s. Aiming for a statistical power of 90% and a significance criterion of 0.05, the calculated sample was 21 patients in each group. To reduce the possibility of dropouts, we enrolled 25 patients per group.

3.1. Statistical analysis

Quantitative data were presented as mean ± standard deviation. Continuous variables were analyzed using one-way ANOVA, and Bonferroni post hoc tests were used to correct for multiple comparisons. While qualitative data were presented by frequency distribution and chi square test was used. The package SPSS 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. $P < 0.05$ was considered statistically significant.

4. Results

Seventy-five patients undergoing vaginal hysterectomy under spinal anesthesia completed this study (Fig. 1). Patients characteristics and duration of surgery in all the three groups were comparable (Table 1). All the groups were comparable with regard to time of onset and grading of shivering. Mean time to cessation of shivering after injection of drug was 1.97 ± 0.61 min in group D while it was 3.56 ± 0.82 min in group N and 12.4 ± 3.74 min in group C which was statistically significant (p value < 0.0001) on intergroup comparison (Table 2). Shivering was controlled in 100% of patients in Dexmedetomidine group compared to 92% of patients in Nalbuphine group and 32% in normal saline group. A statistically significant difference (p value < 0.0001) in success rate was observed when group N and group D were compared to group C (Table 3). Recurrence of shivering was observed in 2/23 patients (8%) in group N, 6/8 patients (75%) in group C compared to none in group D. This difference in relapse rate was insignificant (p value = 0.82) when Nalbuphine group was compared to Dexmedetomidine group, however, statistical significance (p value < 0.0001) when these groups were compared to control group (Table 3).

Among the side effects, one patient (4%) experienced mild nausea in group D, three patients (12%) in group N and two (8%) in group C. This was not found to be statistically significant. Fifteen patients (60%) in group D and 14 patients (56%) in group N had sedation grade 2, while 5 patients (20%) in group D and two patients (8%) in group N had sedation grade 3. Three patients in group D experienced bradycardia which was transient and did not require treatment. Pain during injection was an outstanding complaint in the Nalbuphine group (Table 4).

Heart rate and mean blood pressure were significantly lower in group D compared to the other groups for a period of about 25 min following dexmedetomidine injection (Figs. 2 and 3), but didn't require any treatment. Axillary temperatures and SpO_2 were comparable in the three groups with no significant difference (Figs. 4 and 5).

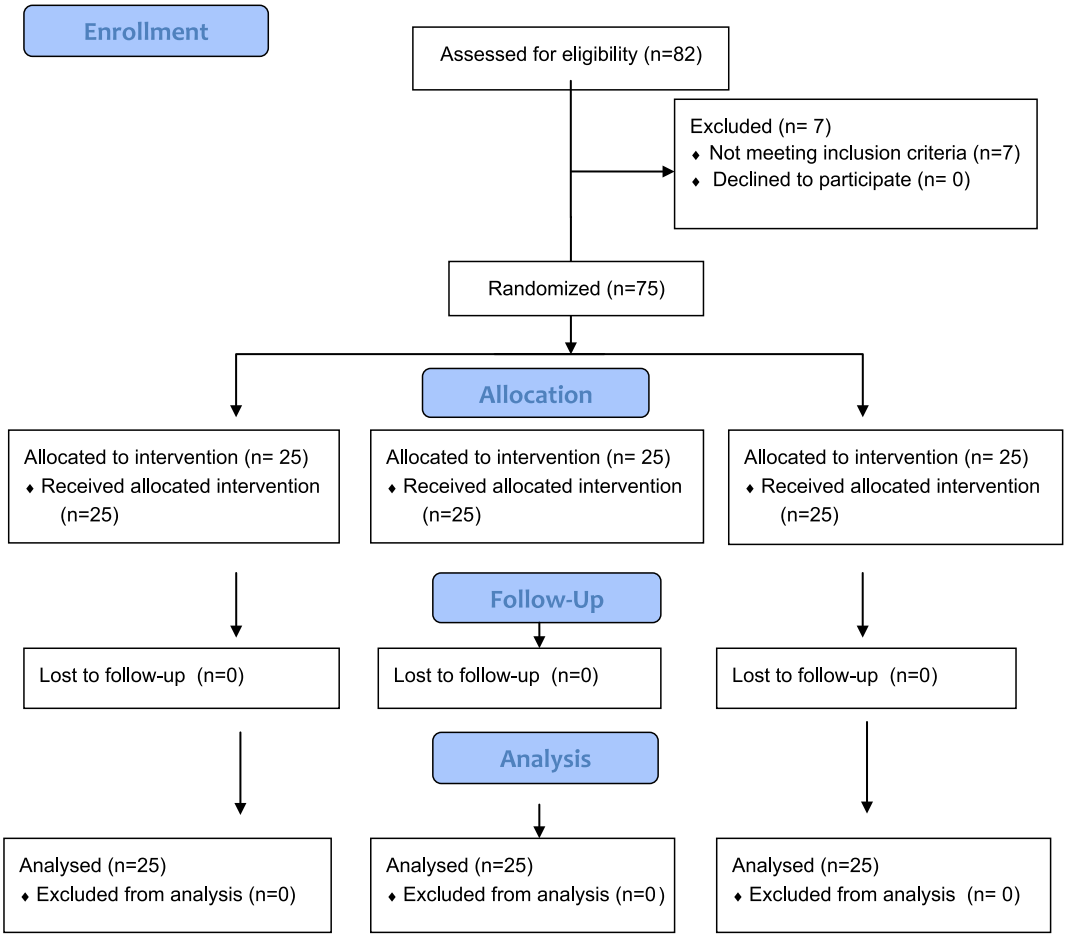

Figure 1. Flow Diagram for participants.

Table 1
Demographic data in the study groups.

Data	Group C (n = 25)	Group N (n = 25)	Group D (n = 25)	P value
Age (years)	55.38 ± 11.64	52.06 ± 13.36	53.25 ± 15.91	0.1
Weight (kg)	75.7 ± 9.5	76.2 ± 6.6	75.7 ± 10.6	0.6
Height (cm)	149.1 ± 7.3	150.9 ± 8.4	152.8 ± 5.8	0.7
ASA (I/II)	20/5	21/4	22/3	0.8
Duration of surgery (min)	94.34 ± 14.53	96.67 ± 12.8	99.32 ± 10.8	0.9
Crystalloid fluids (CC)	2226.85 ± 234.12	2150.25 ± 235.12	2175.25 ± 220.12	0.1
Shivering grade III/IV	III = 16 (64%) IV = 9 (36%)	III = 13 (52%) IV = 12 (48%)	III = 14 (56%) IV = 11 (44%)	0.8

Table 2
Assessment of shivering and response time.

	Group C (n = 25)	Group N (n = 25)	Group D (n = 25)	P value
Onset of shivering (min)	18.45 ± 10.76	18.00 ± 9.37	18.50 ± 11.02	0.95
Time interval from treatment to cessation of shivering (min)	12.4 ± 3.74	3.56 ± 0.82**	1.97±0.61**,#	0.0001

One way ANOVA -test between the three groups followed by Bonferroni post hoc test.
Significance between Nalbuphine group and Dexmedetomidine group. p = 0.04.
** Significance between Control group and group N, D. p = 0.0001.

Table 3
Treatment outcome of shivering in the three groups (number and %).

Data	Group C (n = 25)	Group N (n = 25)	Group D (n = 25)	P value
Success rate	8/25 (32%)	23/25 (92%)	25/25 (100%)	0.0001*
Recurrence after success	6/8 (75%)	2/23 (8.7%)	0/25 (0%)	0.0001*
Failure	17/25 (68%)	2/25 (8%)	0/25 (0%)	0.0001*

Group C = Control, Group N = Nalbuphine, Group D = Dexmedetomidine.
One way ANOVA followed by Post Hoc test was used for analysis.
* Significance between group C and groups N and D.

Table 4
Complications in the three groups (number and %).

Complications	Group C (n = 25)	Group N (n = 25)	Group D (n = 25)	P value		
				C/N	C/D	N/D
Nausea	2(8%)	3(12%)	1(4%)	1.0	1.0	0.921
Sedation						
Grade 1	25	9	5	0.0001	0.0001	0.386
Grade 2	0	14	15	0.0001	0.0001	1.0
Grade 3	0	2	5	0.972	0.046	0.422
Grade 4	0	0	0			
Bradycardia	0	0	3	1.0	0.090	0.090
Hypotension	2	2	3	1.0	1.0	1.0
Pain on injection	0	20(80%)	0	0.0001	1.0	0.0001

Group C = Control, Group N = Nalbuphine, Group D = Dexmedetomidine.
ANOVA followed by Post Hoc test to compare the three groups. C/N: group C versus group N C/D: group C versus group D N/D: Group N versus group D.

5. Discussion

The results of the present study showed the superiority of dexmedetomidine over nalbuphine in treatment of postspinal shivering as shown by a shorter response time, higher success rate and less recurrence.

In our study, a dose of 0.07 mg/kg nalbuphine was used. This dose was chosen on the basis that equianalgesic doses of nalbuphine versus meperidine is 1:5 [8] and, Wrench et al. suggested that the minimal effective dose of meperidine for treating postspinal shivering is approximately 0.35 mg/kg [14]. This dose effectively controlled shivering in 92% of patients with only an 8.7% recurrence rate in the present study.

Kyokong et al. used 0.05 mg/kg to treat shivering following spinal anesthesia for cesarean section. Nalbuphine showed a success rate of 81.4% and a 15.8% recurrence rate [17]. This difference may be attributed to the smaller dose used and the much younger mean age of their study group 29.93 ± 5.3 vs 52.06 ± 13.36 yrs in our groups.

Gotz et al., used 10 mg nalbuphine to treat shivering following general anesthesia and found that nalbuphine suppressed postoperative shivering as effectively and timely as meperidine [18]. Wang et al., used a dose of 0.08 mg/kg to treat shivering following general anesthesia, nalbuphine produced a rapid and potent antishivering effect similar to that observed with meperidine [19].

In the present study, Dexmedetomidine 0.5 μg/kg produced a rapid and effective control of shivering in 100% of patients with

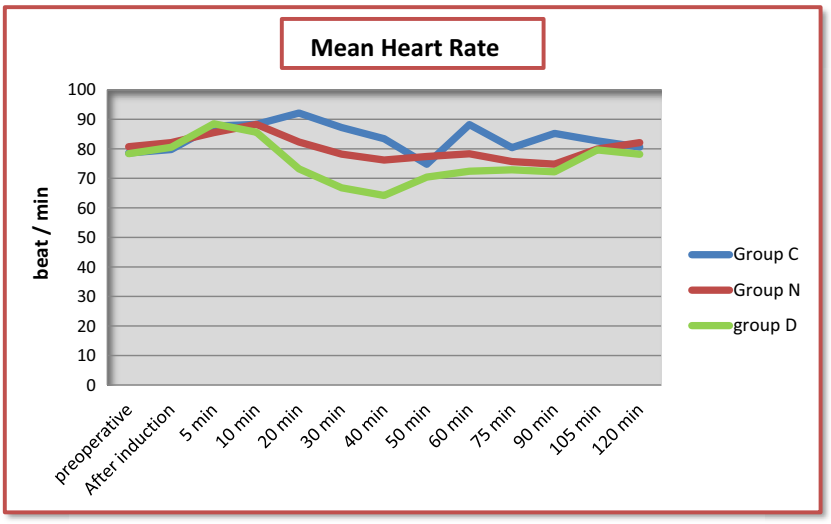

Figure 2. Perioperative changes in heart rate.

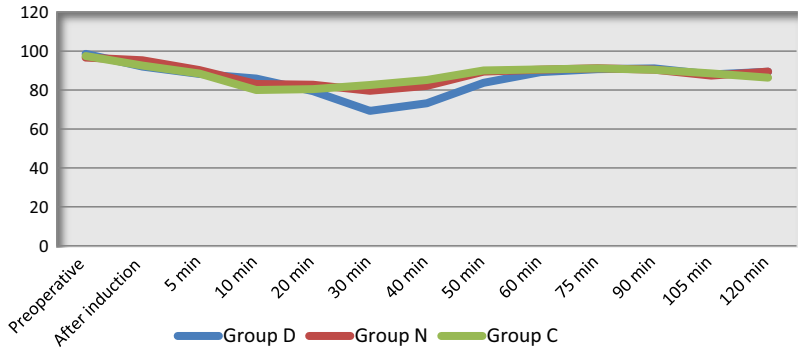

Figure 3. Perioperative changes in mean blood pressure.

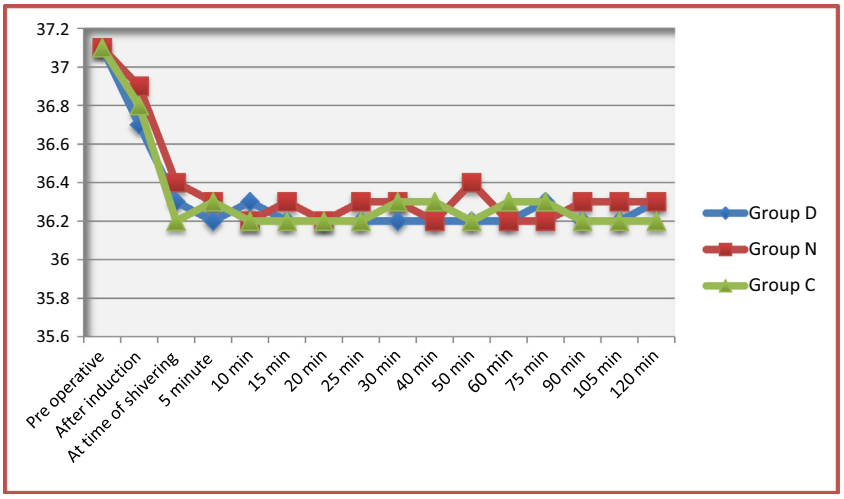

Figure 4. Changes in corrected axillary temperature over time.

no recurrence. This dose was chosen according to the results of a meta-analysis which indicated the minimum effective dose for controlling postoperative shivering to be 0.5 μg/kg [20].

Mittal et al. used dexmedetomidine 0.5 μg/kg for treatment of post spinal shivering. Dexmedetomidine controlled shivering in100% of patients and time for cessation of shivering was 2.52 ± 0.44 min, recurrence occurred in 4% of patients. The incidence of sedation was 21.4% [21].

Blaine Easley et al. reported that dexmedetomidine 0.5 μg/kg as a single IV bolus dose over 3–5 min was effective for treatment of postanesthesia shivering in children following general anesthesia. Cessation of shivering occurred within 5 min after the completion

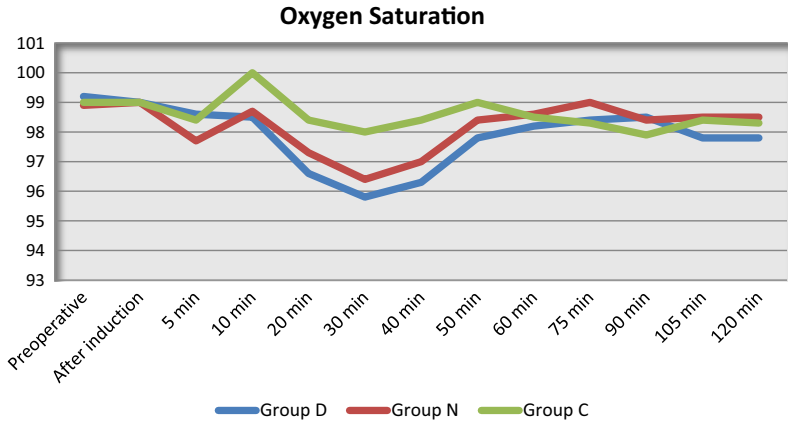

Figure 5. Oxygen saturation over time.

of dexmedetomidine administration. There was no recurrence of shivering and no adverse effects [22].

Sedation accompanied both nalbuphine (64%) and dexmedetomidine (80%) which is actually beneficial during surgery under spinal anesthesia.

Regarding cost/effectiveness, the price of Dexmedetomidine in Egypt (Precedex, 100 μg/ml, 2 ml vial, Hospira) is 170 £ compared to £7 for Nalbuphine (Nalufin 20 mg/ml, Amoun). However, Precedex is a multidose vial, so average patient cost for 0.5 μg/kg would be around £40–45.

A limitation of this study is that we could not measure the core body temperature. For measurement of core body temperature, the probe needs to be put in the esophagus or near the tympanic membrane. Both sites were uncomfortable and unacceptable to patients under spinal anesthesia. Rectal temperature was unaccepted by the surgeon as it would interfere with the surgical field.

6. Conclusion

The limited availability of meperidine provoked a search for effective alternatives. Both nalbuphine and dexmedetomidine control shivering effectively, but dexmedetomidine seems to be a better choice than nalbuphine for treatment of postspinal shivering due to its higher response rate, shorter response time and lower incidence of recurrence. Meanwhile, nalbuphine offers more hemodynamic stability and lower costs.

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