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Research Article

Dexmedetomidine versus Nefopam for the management of post-spinal anesthesia shivering: A randomized double-blind controlled study

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KEYWORDS

Shivering;
Spinal anesthesia;
Dexmedetomidine;
Nefopam

Abstract *Background:* This study is designed to evaluate the relative efficacy of intravenously administered dexmedetomidine and nefopam for control of intraoperative shivering following spinal anesthesia.

Materials and methods: A prospective, randomized, double-blind, controlled study was conducted on 100 ASA grade I and II patients of either sex, aged 18–60 years, scheduled for elective lower abdominal and lower limb surgeries, under spinal anesthesia. Patients who developed post-spinal anesthesia shivering of grade 3 or 4 were included in the study, and randomly allocated to one of two groups, group D (n = 50), received Dexmedetomidine in a dose of 0.5 μg/kg diluted in 10 ml isotonic saline slowly I.V. (one minute duration), and group N (n = 50), received Nefopam in a dose of 0.15 mg/kg diluted in 10 ml isotonic saline slowly I.V. (one minute duration) when shivering was observed. Time taken for control of shivering, response rate, recurrence rate, hemodynamics, time to first request of rescue analgesic, one-patient cost and adverse effects were recorded.

Results: The time taken for control of shivering was statistically significantly shorter in Nefopam group (group N) compared with dexmedetomidine group (group D). The average time taken for disappearance of shivering was 2.35 ± 0.67 min in group N compared with group D (4.63 ± 1.19 min) (p = 0.041). Patients with incomplete response were more in group D (two patients in group D compared with nil in group N), but not statistically significant and recurrence rate was one patient in group D compared with nil in group N. Time to first request to rescue

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analgesic was significantly prolonged in group N (351.24 ± 19.71 min) compared with group D (192.63 ± 9.08 min). One-patient cost was significantly lesser in group N (about two £/patient) compared with group D (about 168 £/patient). Adverse effects such as bradycardia, hypotension and sedation were observed in Dexmedetomidine group, while pain at injection was noted in Nefopam group.

Conclusion: Nefopam is better as compared to dexmedetomidine for control of intraoperative shivering under spinal anesthesia due to its rapid onset, higher response rate, no sedation, lesser hemodynamic alterations, lesser requirements of rescue analgesics and lesser costs.

1. Introduction

Spinal anesthesia is known to significantly impair thermoregulation through inhibiting vasomotor and shivering responses and through redistributing heat from core body to peripheral tissues with subsequent rapid hypothermia during anesthesia [1]. So, shivering, which is defined as an involuntary oscillatory muscular activity, is considered a physiological response to core temperature in an attempt to raise the metabolic heat production and is associated with cutaneous vasodilatation [2]. However, shivering can double or even triple oxygen consumption and carbon dioxide production, triggers myocardial ischemia, causes arterial hypoxemia, increased intraocular and intracranial pressures, increases wound pain, delayed wound healing, and interferes with pulse rate, blood pressure and electrocardiogram (E.C.G.) monitoring [3,4].

Prevention of post-anesthetic shivering (PAS) mainly entails preventing perioperative heat loss by increasing ambient temperature of operative room, using conventional warm air blankets and using warmed intravenous (I.V.) fluids [5].

Although the neurotransmitter pathways involved in the mechanism of PAS are complex and still anonymous, there are various pharmacological drugs available for the management of PAS such as meperidine, clonidine, tramadol and ketamine. However, every drug has its own adverse effect and the ideal anti-shivering still not found [6–8].

Dexmedetomidine is a highly selective α_2-adrenoceptor agonist that has been used as a sedative and is known to reduce shivering threshold [9]. Nefopam is a non-opioid, non-sedative, centrally acting analgesic which is known as an effective for the treatment of shivering [10]. This study is designed to compare the anti-shivering efficacy (primary outcome variable), hemodynamic effects, possible adverse events, time to first rescue analgesic requirements and one-patient cost (secondary outcome variables) with either of Dexmedetomidine or Nefopam during spinal anesthesia.

2. Methods

This prospective, randomized, double-blind, clinical study was conducted at Qena university hospital at the time period from July 2013 to July 2014. The study protocol was approved by the ethics committee of Qena faculty of medicine, and written informed consent was obtained from every patient participating in the study.

This study was registered at ANZCTR with a trial I.D. ACTRN 12614001124628, and website;
http://www.ANZCTR.org.au/ACTRN12614001124628.

A total of one-hundred patients, of either sex, aged 18–60 years, American Society of Anesthesiologists (ASA) grade I and II scheduled for elective lower abdominal and lower limb surgeries under spinal anesthesia were included. Patients with known hypersensitivity to dexmedetomidine or nefopam, cardiopulmonary, renal or hepatic disease, convulsive disorders, glaucoma, senile enlargement of prostate, patients taking tricyclic antidepressants, procedures requiring transfusion of blood or blood products, obese patients (body mass index > 30 kg/m^2), patients with a contraindication to spinal anesthesia, e.g., coagulation disorders, local or general infection, progressive neurological disorders, patients with failed or partial spinal block or those who do not agree to participate in the study were not included in the study.

All patients who fulfilled the inclusion criteria and developed post-spinal anesthesia shivering were enrolled. Randomization method was done according to computer generated random table. Allocation concealment was done using closed envelops to randomize the patients into two groups: Group D (n = 50) where Dexmedetomidine was administered at a dose of 0.5 μg/kg I.V. (Precedex®) and Group N (n = 50) who received Nefopam in a dose of 0.15 mg/kg I.V. (Nopain®). Each drug was diluted into 10 ml by isotonic saline and given by slow I.V. (one minute-duration) at the start of shivering. In order to facilitate blinding, the test solution was prepared by the first anesthesiologist who is not involved in the study. Neither the recording (second) anesthesiologist nor the patients were aware of the kind of the drug.

Upon arrival into the operative room, a 20-Gauge venous cannula was inserted and a preload of 1000 ml. Ringer's lactate solution was infused for 1 h before initiation of spinal anesthesia and maintained at 6 ml/kg/h after spinal anesthesia. Standard monitors were applied and all baseline parameters such as heart rate (H.R.), non-invasive blood pressure (NIBP), oxygen saturation (SpO2), electrocardiography (E.C.G.) and axillary temperature were recorded before the start of surgery and thereafter at every 15 min for 1 h and every 30 min for the rest of observation period.

Under complete septic precautions, patients were placed in the sitting position and anesthetized locally with Lidocaine 2%, 2 ml. At the level of $L_{3\text{-}4}$ interspace using a 25-Gauge Quinckie spinal needle (Becton, Dicknson™, Spain). After confirming clear and free flow of C.S.F., all patients in the two groups received drug volume of 3 ml containing 15 mg hyperbaric bupivacaine hydrochloride (Marcaine® Spinal heavy 0.5%, AstraZeneca, Istanbul, Turkey). The level of spinal block was determined by pinprick at the mid-axillary line after 5 min following spinal anesthesia. When a block of T10 level was achieved, patients were prepared for operation.

Operative room was maintained at an ambient temperature of around 24–25 °C for all patients participating in the study. Oxygen was administered to all patients at a rate of 4 L/min with Hudson facemask and the patients were covered with drapes. I.V. fluids and anesthetics were administered at room temperature.

Shivering was graded using a four point scale as per Wrench et al. [11];

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 anesthesiologist recorded the time in minutes at which shivering started after spinal anesthesia (onset of shivering), severity of shivering, time to disappearance of shivering and response rate. Duration of surgery was recorded and duration of spinal anesthesia was noted by assessing spontaneous recovery of sensory block using the pin-prick method and observing spontaneous movements of limbs in the post-operative period. If shivering recurs, patients were treated with an additional dose of Dexmedetomidine (0.5 μg/kg) or Nefopam (0.15 mg/kg) in the respective groups by the same way mentioned previously and recorded. The degree of sedation was evaluated with a four-point scale as per Filos et al. [12];

1 – awake and alert; 2 – drowsy, responsive to verbal stimuli; 3 – drowsy, arousable to physical stimuli; 4 – unarousable. This monitoring is continued in the post-operative period till 2 h after spinal block.

Adverse effects such as nausea, vomiting, severe bradycardia (< 50/min), hypotension (> 20% of baseline), pain at I.V. injection and sedation score were recorded. Time to first rescue analgesic medication (ketolorac I.V. 30 mg) and one-patient costs for control of PAS were recorded.

3. Sample size

Sample size calculation was done using online power/sample size calculator (http://www.stat.ubc.ca). The means of time taken for cessation of post-spinal shivering after treatment

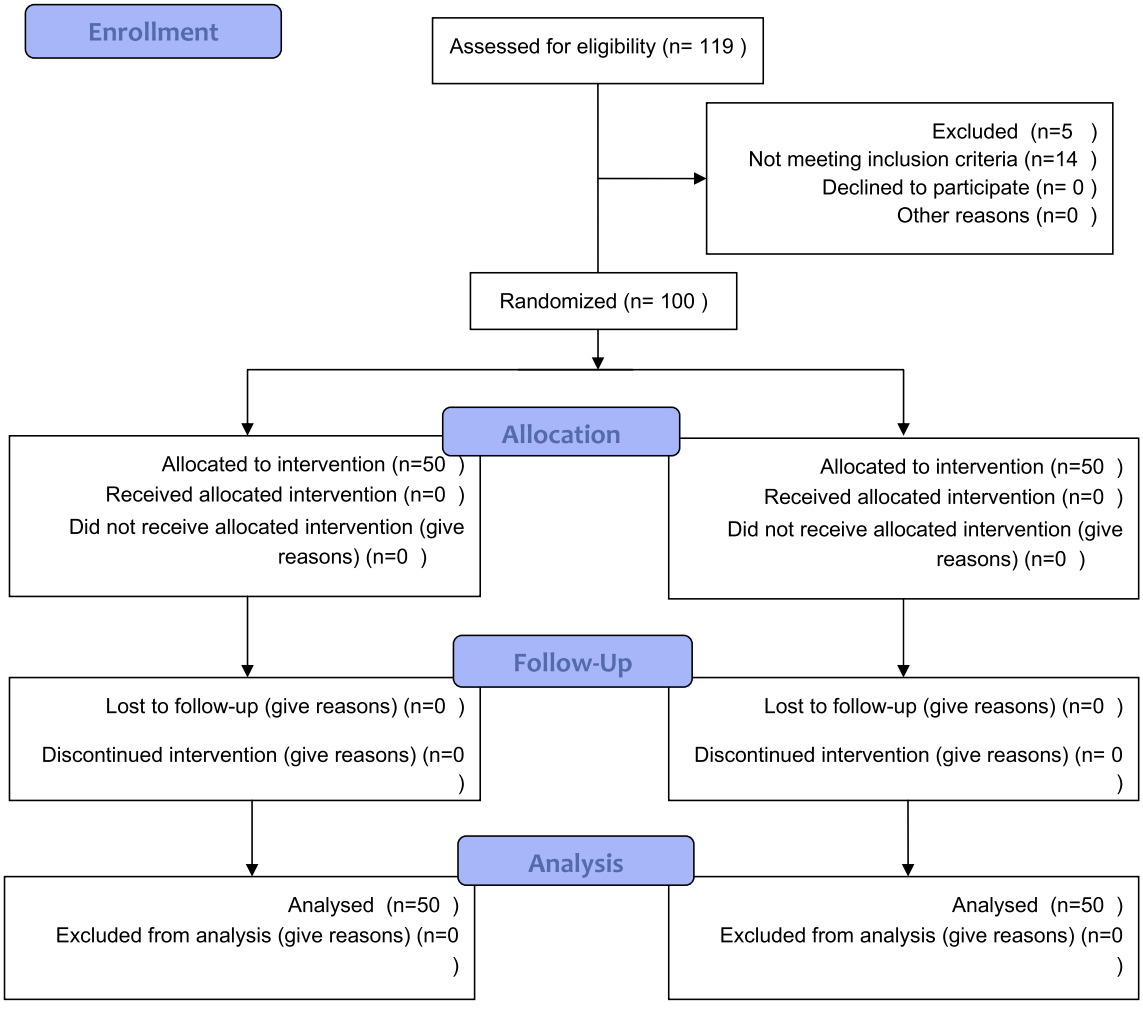

Figure 1 The study flow diagram.

with either Dexmedetomidine or Nefopam was considered the primary end point of this study. We hypothesized that detectable difference between the means of time taken for cessation of post-spinal shivering after treatment with either of both drugs = 180 s. If we estimated a standard deviation (S.D.) for this prospective power analysis as 20% and an α-value of 0.05, the power of study would be 90%, sample size calculated to be 44 patients per group. To reduce the possibility of drop-outs, we enrolled 50 patients per group.

4. Statistical analysis

Statistical analysis was performed using SPSS statistical package version 20 (SPSS Inc., Chicago, IL). Numerical data were presented as mean ± S.D. and categorical data as proportions (%). The unpaired *t*-test was used for comparison of the means of all variables between the two groups. *P* value of <0.05 was considered statistically significant.

5. Results

A total of 100 patients were enrolled in the present study and were randomized into two groups of 50 each ($n = 50$) (Fig. 1). Both groups were comparable with respect to age, gender, weight, ASA grade, duration and type of surgery, volume of intravenous fluid administered and duration of spinal anesthesia (Table 1). Also, axillary temperature was comparable in both groups during the observation period. Heart rate was significantly lower in Dexmedetomidine group compared with Nefopam group during the study period (Fig. 2). However, there is no evidence of severe bradycardia (H.R. < 50/min) in any of the studied patients. Mean arterial pressure (MAP) was significantly lower in Dexmedetomidine group compared with Nefopam group till 60 min after spinal block, but increased thereafter (Fig. 3).

Table 1 Demographic profile of patients of both groups.

Parameter	Dexmedetomidine group ($n = 50$)	Nefopam group ($n = 50$)	*P* value
Age (years)	37.4 ± 9.8	35.7 ± 8.7	0.693
Gender (M/F)	36/14	35/15	0.549
Weight (kg)	71.6 ± 8.6	73.3 ± 9.4	0.427
Height (cm)	173.6 ± 7.3	171.7 ± 6.5	0.329
ASAI/ASAII	35/15	37/13	0.482
Duration of surgery (min)	87.4 ± 12.73	83.7 ± 9.12	0.427
Duration of spinal anesthesia (min)	136.2 ± 14.1	132.7 ± 11.6	0.295
Crystalloids infused (c.c)	1553 ± 527.2	1483 ± 392.7	0.372

Data are presented as mean ± SD, number. n = number of patients.
M/F = males/females, ASA = American Society of Anesthesiologists physical status.
There were no statistically significant differences between the two groups with respect to demographic data, patient's characteristics related to spinal anesthesia, duration of surgery and sensory block level.

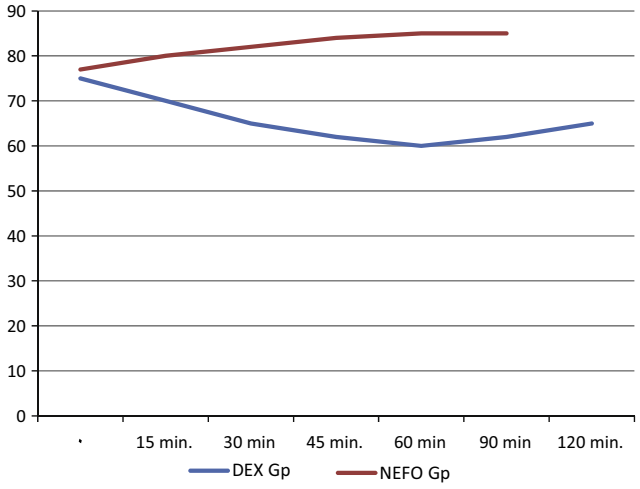

Figure 2 Perioperative heart rate changes in both groups.

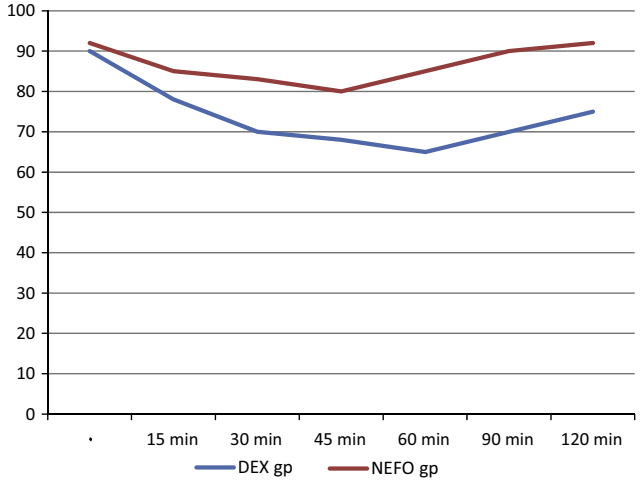

Figure 3 Perioperative MAP changes in the two studied groups.

Table 2 Parameters for post-spinal anesthesia shivering.

Parameter	Dexmedetomidine group ($n = 50$)	Nefopam group ($n = 50$)	*P* value
Onset of shivering	11.7 ± 5.2	12.3 ± 5.8	0.692
Time for cessation of shivering after medical treatment (min)	4.63 ± 1.19	2.35 ± 0.67*	0.031
Response rate	48 (96%)	50 (100%)	0.492
Incomplete response	2 (4%)	0	0.168
Recurrence	1 (2%)	0	0.275

Data are presented as mean ± S.D., number and percentage (%).
* Significant.

Shivering disappeared in 48 (96%) patients who received Dexmedetomidine and 50 (100%) patients who received Nefopam (Table 2). Both drugs were found to be effective in

reducing shivering. However, incomplete response to therapy was observed in two patients (4%) in Dexmedetomidine group who was given a rescue dose of Dexmedetomidine (Table 2).

There was no statistically significant difference regarding the time for onset of shivering between the two groups. However, the mean time interval between the administration of drug after onset of shivering and disappearance of shivering was significantly shorter in the Nefopam group (2.35 ± 0.67 min) compared with Dexmedetomidine group (4.63 ± 1.19 min) ($p = 0.031$) (Table 2).

Adverse effects such as hypotension, bradycardia and sedation were observed in Dexmedetomidine group while pain at injection was noted in Nefopam group (Table 3).

Time to first rescue analgesic was significantly prolonged in Nefopam group (351.24 ± 19.71 min) compared with Dexmedetomidine group (162.63 ± 9.08 min) and also one-patient costs for control of PAS were cheaper significantly with Nefopam group (2 £/patient) compared with Dexmedetomidine group (168 £/patient) (Table 4).

6. Discussion

Since proper control of PAS necessitates a drug which is not only effective but also with rapid onset, minor adverse effects, simple and inexpensive, the results of the present study showed the superiority of Nefopam over Dexmedetomidine for the management of post-spinal anesthesia shivering, although both drugs were nearly equally effective in the control of shivering, as the time taken for control of shivering was statistically significantly lower in Nefopam group (2.35 ± 0.67 min) compared with Dexmedetomidine group (4.93 ± 0.93 min) [$p = 0.031$]. Bilotta et al. [10] first reported that nefopam was superior to tramadol for the prevention of shivering during neuraxial anesthesia. Also, Piper et al. [13] reported that nefopam is better than clonidine for the prevention of postanesthetic shivering whereas Kim et al. reported that prophylactic administration of nefopam reduces the incidences and scores of shivering during spinal anesthesia similar to meperidine [14]. Furthermore, nefopam maintained heart rate and mean arterial pressure and this is not surprising as nefopam is known to have positive inotropic and chronotropic effects. While most antishivering drugs reduce both the thresholds of shivering and vasoconstriction, Alfonsi et al. [15] reported that nefopam significantly reduced only the shivering threshold. Maintaining higher blood pressure may be due to the nefopam sparing vasoconstriction threshold. Another advantage of nefopam is that it did not induce sedation at all. This means that nefopam can be used safely in critically ill patients with hemodynamic instability because the risks of sedation and hypotension can be negated.

Table 3 Incidence of adverse effects in both groups.

Parameter	Dexmedetomidine group ($n = 50$)	Nefopam group ($n = 50$)	P value
Nausea	0	0	
Vomiting	0	0	
Pain on injection	0	3 (6%)	0.052
Sedation	12 (24%)	0	0.013
Hypotension	5 (10%)	0	0.041
Bradycardia	7 (14%)	0	0.034
Respiratory depression	0	0	
Tachycardia	0	0	

Data are presented as the number of patients (percentage).

Table 4 Time to first rescue analgesic and one-patient cost in both groups.

Parameter	Dexmedetomidine group ($n = 50$)	Nefopam group ($n = 50$)	P value
Time to 1st rescue analgesic (min)	162.63 ± 9.08	351.24 ± 19.71*	0.004
One-patient cost (£)	168	2**	0.0004

Data are presented as mean ± SD.
* Significant.
** Highly significant.

Nefopam is a non-opioid centrally-acting analgesic. Its chemical structure is benzoxazocine which is structurally related to diphenhydramine (an antihistaminic drug) and orphenadrine (an anti-muscarinic drug). It is used mainly as an analgesic drug for relief of moderate to severe pain as an alternative to opioids. It inhibits the synaptosomal uptake of serotonin, norepinephrine and dopamine, and interacts directly with α_2-adrenoceptors [16], and non-competitive NMDA antagonist [17]. The additional antishivering effect is related to the inhibition of monoamine and NMDA receptors.

Contradictory to the present study, Mittal and colleagues reported that the time taken for cessation of shivering was less with dexmedetomidine (2.52 ± 0.44 min) when compared to tramadol in patients scheduled for various surgeries under spinal anesthesia although both drugs were effective for control of shivering. Moreover, dexmedetomidine had shown negligible adverse effects, whereas tramadol is associated with significant nausea and vomiting [18]. The rate of I.V. injection of dexmedetomidine and the sample size may be the cause of difference in the time taken for cessation of shivering in both studies.

The action of dexmedetomidine appears to be due to central thermoregulatory inhibition because it comparably reduces both vasoconstriction and shivering thresholds [19]. The hemodynamic effects of dexmedetomidine are biphasic as when it is administered I.V., it causes hypotension and bradycardia until central sympathomimetic effect achieved, and then it causes moderate decreases in MAP and H.R. [20] and this explains the drop of B.P. and reduction in H.R. observed in the dexmedetomidine group compared with the nefopam group. Sedation more than grade two occurred in 12 patients (24%) in dexmedetomidine group which were in accordance with the previous studies [9,21]. One contradictory report was by Karaman et al. according to whom intraoperative dexmedetomidine infusion caused negligible sedation in spite of using a loading dose of 1 UG/kg followed by a maintenance infusion of 0.5 UG/kg/h [22].

Time to first rescue analgesic was significantly prolonged in the nefopam group compared with dexmedetomidine group and this can be attributed to its strong analgesic properties [16] and this result agreed with other results that proved the efficacy of nefopam as analgesic [23]. Also, control of PAS

with nefopam was significantly cheaper compared with dexmedetomidine and this is of considerable interest in controlling hospital costs.

Pain at injection is observed in five patients (10%) in the nefopam group and it is considered to be related to the way of administration of nefopam and it resolved spontaneously in all patients within 5 min.

The limitations of the present study are short duration surgeries, as the anti-shivering effect of dexmedetomidine needs to be observed in surgeries of long duration where hypothermia is more evident and the core temperature not measured. Also, some bias may be present as most surgeries performed are one-day surgery performed under spinal anesthesia which necessitates rapid recovery of patients. Additionally, we did not assess different doses of dexmedetomidine.

To conclude, both nefopam and dexmedetomidine are effective for control of shivering under spinal anesthesia. However, nefopam is better as compared to dexmedetomidine due to rapid onset, higher response rate, absence of sedation and hemodynamic alterations, lesser doses of second rescue analgesic allover 24 h and lesser one-patient costs. Further studies to prevent injection pain of nefopam are required.

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Conflict of interest

The author declares no conflict of interest.

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