

Efficacy of Intravenous versus Intrathecal Meperidine on Post-Spinal Shivering after Knee Arthroscopy: A Randomized Controlled Study

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Abstract

Background and Aims: Hypothermia is considered a common problem with anesthesia. Spinal anesthesia, affects the process of temperature regulation. The aim of this study was to compare the prophylactic effect of intravenous (IV) meperidine with intrathecal (IT) meperidine on the prevention of shivering during spinal anesthesia in patients underwent knee arthroscopy. **Aim of the Study:** The aim of this work is to study the effect of meperidine either intravenous (IV) vs intrathecal (IT) on controlling postoperative shivering after knee arthroscopy. **Materials and Methods:** This study will be conducted in accordance with the principles of the ethics committee Benha University hospitals. Full written informed consent will be obtained from all patients before inclusion in the study, and a prospective randomized double-blinded study was conducted in adult patients undergoing knee arthroscopy under spinal anesthesia. Cases are divided into three equal groups (20 patients in each). Group IT: will receive spinal anesthesia (12.5 mg heavy bupivacaine) with intrathecal meperidine (25 mg). Group IV: will receive spinal anesthesia (12.5 mg heavy bupivacaine) with intravenous meperidine (25 mg). Group C: will receive spinal anesthesia (12.5 mg heavy bupivacaine) only postoperatively. Incidence and degree of shivering (SS), sedation score (RSS), pain score (VAS), hemodynamics, and PONV will be measured at the following intervals: 0 min (once arrived at PACU), 20 min later, 40 min later, 80 min later. **Results:** Shivering was observed in 0%, 0%, and 10.5% of patients in Groups IT, IV, and C, respectively. There was a significant difference between Group IT and IV compared to Group C ($P < 0.001$). Shivering incidence and intensity in IT group and IV group was significantly lower than C group ($P < 0.001$). There was a better postoperative pain control in IT group than IV group, and also IT group was showed less side effects as it showed less PONV than IV group. **Conclusion:** We concluded that IT meperidine and IV mepe-

ridine comparably can decrease intensity and incidence of shivering compared to control group as well as decrease the requirement for additional doses of meperidine for shivering control without any hemodynamic side effect. And intrathecal meperidine showed better postoperative pain control and less postoperative nausea and vomiting (PONV).

Keywords

Shivering, Meperidine, Spinal Anesthesia, Knee Arthroscopy

1. Introduction

Shivering is a function of the body in response to cold in warm-blooded animals. When the core body temperature drops, the shivering reflex is triggered to maintain homeostasis [1] [2] [3] [4].

Morphine, fentanyl, alfentanil, ondansetron, Zofran, clonidine and meperidine are most commonly used for shivering, with meperidine as perhaps the most effective one [5].

The anti-shivering effect of meperidine exactly is still unknown, but may involve the stimulation of κ -opioid receptors [6].

Regional anesthesia affects the process of temperature regulation [7]. Shivering with more than 55% incidence is common and unpleasant complications of spinal anaesthesia [8] [9] [10] [11].

Although, the exact mechanism of shivering following SA is unknown; theories such as heat loss during surgery, increased sympathetic tone, pain, and released systemic pyrogens have been related [8] [10].

For a long period, intravenous (IV) meperidine has been used for the treatment and prevention of shivering during surgery and emergence [10] [11] [12].

Meperidine in equivalent dose is more effective when compared with other μ -opioid receptor agonists such as fentanyl, alfentanil, sufentanil, and morphine. [12] [13]. It seems that IV meperidine exerts its anti-shivering effects via the activation of kappa-opioid receptors [14] [15] [16].

Intrathecal meperidine, dosage as low as 0.2 mg/kg or 12.5 mg, was reported to show an anti-shivering effect without nausea or vomiting [16] [17] [18].

2. Patient and Methods

This study will be conducted in accordance with the principles of the ethics committee Benha University hospitals. Full written informed consent will be obtained from all patients before inclusion in the study.

2.1. Methodology

1) Study Design:

Randomized controlled study.

2) Study Setting and Location:

Operating theatres in Benha University hospitals.

3) Study Population:

Adult patients undergoing knee arthroscopy under spinal anesthesia.

4) Eligibility Criteria:

a) Inclusion criteria:

- Age from 18 years to 45 years.
- ASA I-II.

b) Exclusion criteria:

- Refusal of patients.
- Patients aged above 45 years and below 18 years.
- Patients with hypersensitivity to the study drug.
- BMI \geq 30.

5) Study Procedures:

a) Randomization:

Randomization will be done using a computer-generated sequence. Concealment will be achieved by the use of opaque envelopes. The study drugs will be prepared by a research assistant in similar syringes to ensure the physician blinding to the drug.

b) Grouping:

In this study, patients will be randomized into three groups:

- Group IT (intrathecal meperidine) (n = 20).
- Group IV (intravenous meperidine) (n = 20).
- Group C (control group) (n = 20).

c) Study Protocol:

A written informed consent will be obtained from all the patients. On arrival to the preparation room, intravenous cannula will be inserted, no sedation will be given. In the operating theater standard monitors, non-invasive blood pressure, oxygen saturation and electrocardiogram will be applied before spinal anaesthesia and baseline heart rate (HR), mean arterial blood pressure (MAP) and oxygen saturation (SpO₂) will be recorded.

All patients in both groups will receive standardized anesthetic technique in the form of spinal anaesthesia in the sitting position after complete strict aseptic technique in L 3-4 interspace.

Intraoperative HR, MAP, EtCO₂ and SpO₂ values will be recorded at 5-minute intervals till the end of operation. HR and MAP will be maintained within \pm 20% of the baseline values. Hypotension (defined as MAP < 20% of the baseline value) will be treated by a bolus of 200 ml Ringer's solution if not responding increments of 3 - 9 mg ephedrine will be given. Hypertension (defined as MAP > 20% of the baseline value). Bradycardia (HR < 50 beat per minute) persisting for > 2 min will be treated with atropine, 0.4 mg i.v. boluses.

By the end of surgery, the patient will be transferred to the post-anesthesia care unit (PACU), and the smoothness of extubation will be assessed immediately after extubation and every 10 minutes until first hour after extubation, SpO₂ and HR will be documented preoperatively as baseline, every 5 min; intra-

operatively and in PACU. Pain will be evaluated using Visual Analogue Scale (VAS) for pain (0 = no pain to 10 = the worst pain); every 2 h in the first 6 hours, if VAS > 4, supplemental doses of 2 mg morphine in both groups will be given. Total amount of narcotics will be recorded.

Any episode of shivering will be recorded according to shivering score (SS): “0” indicated no shivering; “1”, piloerection or peripheral vasoconstriction, but no visible shivering; “2”, muscular activity in only 1 muscle group; “3”, muscular activity in >1 muscle group, but not generalized; and “4”, shivering involving the whole body [12].

Level of sedation will be assessed every 30 minutes in the PACU using Ramsey sedation score (RSS) [11]: 1) Anxious, agitated or restless; 2) Cooperative and oriented; 3) Responsive to commands; 4) Asleep, but response to light glabellar tap or loud auditory; 5) Asleep, sluggish response to glabellar tap or auditory response; and 6) Asleep, no response. An independent, trained nurse blinded to the study drugs being received will assess pain, level of sedation, hemodynamic variables and nausea and/or vomiting. Postoperative analgesic regime will be given as follow: 1 gm paracetamol every 6 hours and 30 mg ketorolac every 12 hours and rescue analgesic is meperidine 0.5 mg/kg.

d) Measurement tools:

Demographics (age - gender - history of chronic illness).

6) Study outcomes:

a) Primary outcome

Incidence and degree of shivering.

b) Secondary outcome(s)

Sedation score, hemodynamics, VAS, duration of surgery, PONV.

2.2. Statistical Analysis

1) Sample size: Power analysis will be performed using G-power 3.1 software. Incidence of shivering will be the main outcome variable in the present study. We will include with 20 patients in each group and we will consider the first 6 patients in the control group as a pilot study and will be used to calculate the mean and standard deviation of incidence of shivering as we expecting 30% difference in incidence of shivering between the control (C) and intrathecal (IT) & intravenous (IV) groups, number of patients will be readjusted accordingly.

2) Statistical analysis:

Statistical analysis will be done using SPSS software. Data will be presented as numbers (%) {for categorical data}, mean (standard deviation) for normally distributed continuous data, median (quartiles) for skewed data. Normality will be checked using Shapiro test. Analysis will be done using chi square, mixed design analysis of variance (ANOVA), and Kruskal Wallis as appropriate. p value will be considered statistically significant.

2.3. Results

The age and weight were comparable in the three groups (**Table 1**). AS regard age,

weight and sex. There was no significant difference in attenuating post-operative shivering at all intervals.

As regard the shivering scale (SS) showed in (Table 2).

There was a significant difference between the control group and other two groups (IT and IV groups).

But there was no significant difference between intrathecal (IT) group and intravenous (IV) group at different intervals.

As regard the shivering scale (SS) showed in (Figure 1).

There was a significant difference between the control group and other two groups (IT and IV groups).

But there was no significant difference between intrathecal (IT) group and intravenous (IV) group at different intervals.

Table 1. Demographic data with median and IQR.

	IT group (20)		IV group (20)		C group (20)		Statistical test (KW)	P value	MWU
	Median	IQR	Median	IQR	Median	IQR			
Age	23.0	21.0 - 28.0	26.0	22.25 - 35.0	23.0	21.0 - 28.0	2.11	0.35	
Wt	65.0	65.0 - 72.0	66.5	64.0 - 70.75	65.0	65.0 - 72.0	0.06	0.97	
BMI	24.0	22.0 - 25.0	25.0	22.0 - 27.0	24.0	22.0 - 25.0	2.12	0.35	

Table 2. Shivering score (SS) in the three groups at different intervals.

SS	IT group (20)		IV group (20)		C group (20)		Statistical test (KW)	P value	MWU
	Median	IQR	Median	IQR	Median	IQR			
0	0.0	0.0 - 1.0	0.0	0.0 - 0.75	2.5	2.0 - 3.0	35.16	<0.001	bc
20	0.0	0.0 - 0.0	0.0	0.0 - 0.0	2.0	2.0 - 3.0	37.76	<0.001	bc
40	0.0	0.0 - 0.0	0.0	0.0 - 0.0	2.0	1.0 - 2.0	47.84	<0.001	bc
80	0.0	0.0 - 0.0	0.0	0.0 - 0.0	1.0	1.0 - 2.0	39.01	<0.001	bc

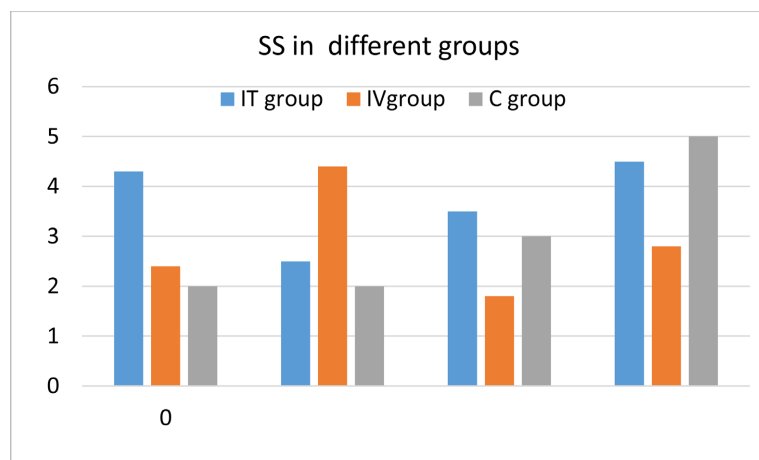
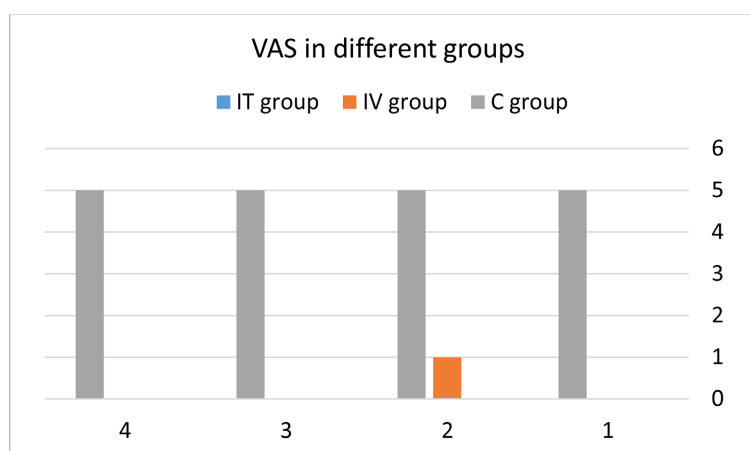


Figure 1. Shivering score (SS) in the three groups at different intervals.

Table 3. Visual analogue scale (VAS) in the three groups at different intervals.

	IT group (20)		IV group (20)		C group (20)		Statistical test (KW)	P value	MW U
	Median	IQR	Median	IQR	Median	IQR			
VAS									
0	0.0	0.0-1.0	0.0	0.0-1.0	5.0	4.0-5.0	42.30	<0.001	bc
20	0.0	0.0-1.0	1.0	0.0-1.0	5.0	4.0-5.0	41.14	<0.001	bc
40	0.0	0.0-0.0	0.0	0.0-0.75	5.0	4.0-5.0	45.79	<0.001	bc
80	0.0	0.0-0.0	0.0	0.0-0.75	5.0	4.24-6.0	46.10	<0.001	bc

**Figure 2.** Visual analogue scale (VAS) in the three groups at different intervals.

As regard the visual analogue scale (VAS) showed in (Table 3).

There was a significant difference ($p < 0.001$) between the control group and other two groups (IT and IV groups) and there was a significant difference ($p < 0.001$) between intrathecal (IT) group and intravenous (IV) group at different intervals. As there was a better postoperative pain control in IT group than IV group, especially at 40 min., and 80 min postoperatively.

As regard the visual analogue scale (VAS) showed in (Figure 2).

There was a significant difference ($p < 0.001$) between the control group and other two groups (IT and IV groups) and there was a significant difference ($p < 0.001$) between intrathecal (IT) group and intravenous (IV) group at different intervals. As there was a better postoperative pain control in IT group than IV group.

As regard the Ramsay sedation score (RSS) showed in (Table 4).

There was no significant difference between intrathecal (IT) group, intravenous (IV) group, and control (C) group at different intervals.

As regard the Ramsay sedation score (RSS) showed in (Figure 3).

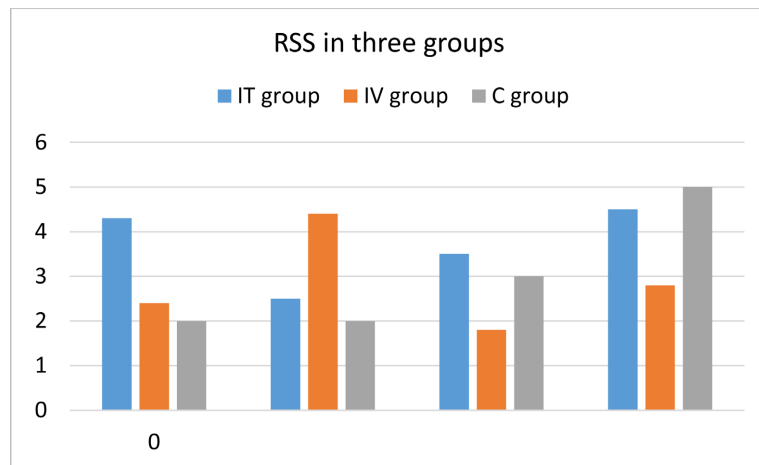
There was no significant difference between intrathecal (IT) group, intravenous (IV) group, and control (C) group at different intervals.

As regard the bradycardia (VAS) showed in (Table 5).

There was a significant difference between the control group and other two

Table 4. Ramsay sedation score (RSS) in the three groups at different intervals.

	IT group (20)		IV group (20)		C group (20)		Statistical test (KW)	P value	MWU
	Median	IQR	Median	IQR	Median	IQR			
RSS									
0	2.0	2.0 - 2.0	2.0	2.0 - 3.0	2.0	2.0 - 2.0	12.03	0.002	bc
20	2.0	2.0 - 3.0	2.0	2.0 - 3.0	2.0	1.0 - 2.0	21.12	<0.001	bc
40	2.0	2.0 - 3.0	2.0	2.0 - 3.0	2.0	2.0 - 2.0	11.12	0.004	bc
80	2.0	2.0 - 2.0	2.0	2.0 - 2.75	2.0	1.25 - 2.0	12.76	0.002	bc

**Figure 3.** Ramsay analogue scale (RSS) in the three groups at different intervals.**Table 5.** Bradycardia in the three groups at different intervals.

	IT group (20)		IV group (20)		C group (20)		Statistical test (KW)	P value	MWU
	Median	IQR	Median	IQR	Median	IQR			
Bradycardia									
0	76.5	68.0 - 82.0	74.5	66.0 - 82.0	77.5	68.25 - 80.75	0.48	0.79	
20	76.0	74.0 - 81.0	75.0	68.0 - 81.0	82.0	80.25 - 84.75	17.19	<0.001	bc
40	78.0	69.0 - 79.75	75.5	65.0 - 80.0	83.0	81.0 - 86.0	26.60	<0.001	bc
80	78.0	71.0 - 82.0	77.0	66.0 - 79.0	81.0	79.0 - 84.75	9.78	0.008	bc

groups (IT and IV groups) in two intervals only (20 min and 40 min).

But there was no significant difference between the control (C) group and other two groups, intrathecal (IT) group and intravenous (IV) group at two intervals (0 min and 80 min).

As regard the bradycardia (VAS) showed in (Figure 4) there was a significant difference between the control group and other two groups (IT and IV groups) in two intervals only (20 min and 40 min).

But there was no significant difference between the control (C) group and other two groups, intrathecal (IT) group and intravenous (IV) group at two in-

tervals (0 min and 80 min).

As regard the hypotension showed in (Table 6).

There was no significant difference between intrathecal (IT) group, intravenous (IV) group, and control (C) group at all different intervals.

As regard the hypotension showed in (Figure 5), there was no significant difference between intrathecal (IT) group, intravenous (IV) group, and control (C)

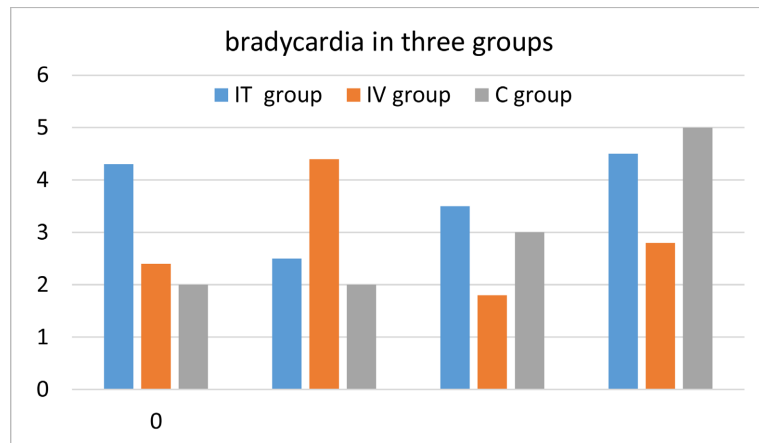


Figure 4. Bradycardia in the three groups at different intervals.

Table 6. Hypotension in the three groups at different intervals

	IT group (20)		IV group (20)		C group (20)		Statistical test (KW)	P value	MWU
	Median	IQR	Median	IQR	Median	IQR			
Hypotension									
0	71.0	55.0 - 79.0	71.0	55.0 - 79.0	75.0	59.0 - 85.75	1.06	0.59	
20	65.0	64.0 - 77.0	65.0	64.0 - 77.0	71.0	64.25 - 82.25	1.42	0.49	
40	68.0	61.0 - 78.0	68.0	60.25 - 78.0	73.0	62.0 - 84.75	0.57	0.75	
80	66.0	62.0 - 85.0	66.0	62.0 - 86.5	75.5	63.0 - 86.5	1.08	0.58	

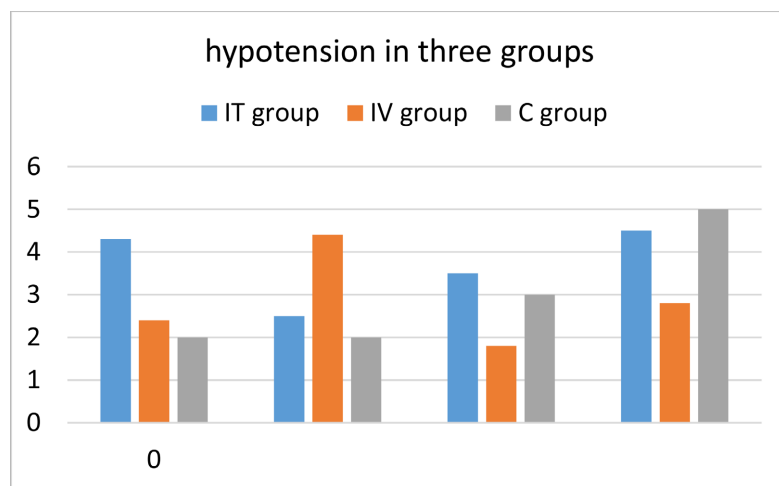


Figure 5. Hypotension in the three groups at different intervals.

group at all different intervals.

As regard the postoperative nausea and vomiting (PONV) showed in (Table 7).

There was a significant difference (p value 0.03) between intrathecal (IT) group, and intravenous (IV) group, at all different intervals. Intrathecal (IT) group showed less side effects as PONV less occurred in this group than IV group and C group at 0, 20, 40, and 80 min postoperatively.

As regard the postoperative nausea and vomiting (PONV) showed in (Figure 6).

There was a significant difference (p value 0.03) between intrathecal (IT) group, and intravenous (IV) group, at all different intervals. Intrathecal (IT) group showed less side effects as PONV less occurred in this group than IV group and C group at 0, 20, 40, and 80 min postoperatively.

3. Discussion

Shivering is a usual and current problem after surgery under spinal anesthesia. Exact mechanism of the shivering after spinal anesthesia has not been completely investigated. Only There are some hypotheses in this object: [19] [20]

As regard to previous studies, IV meperidine for shivering removing has shown

Table 7. Postoperative nausea and vomiting (PONV) in the three groups at different intervals.

	IT group (20)		IV group (20)		C group (20)		Statistical test (KW)	P value	MWU
	Median	IQR	Median	IQR	Median	IQR			
PONV									
0	3	15.0	11	55.0	8	40.0	X2 = 7.03	0.03	
20	1	5.0	6	30.0	8	40.0	X2 = 6.93	0.03	
40	0	0.0	3	15.0	7	35.0	FET = 6.51	0.04	
80	0	0.0	0	0.0	5	25.0	FET = 7.04	0.03	

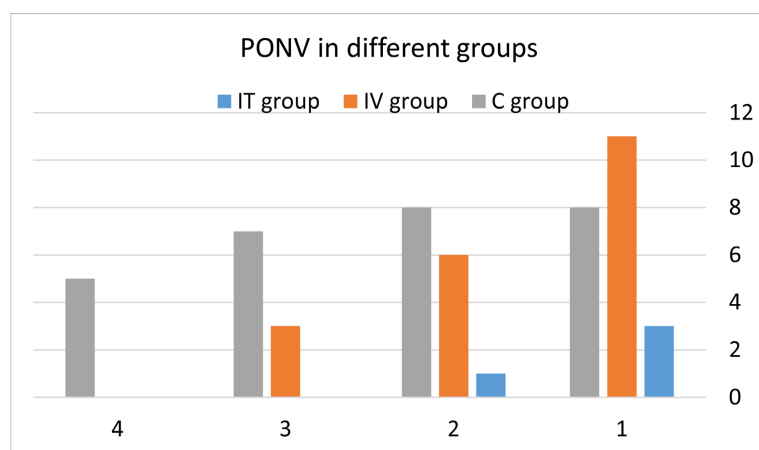


Figure 6. Postoperative nausea and vomiting (PONV) in the three groups at different intervals.

some side effects and other problems of opioids like nausea, vomiting, itching, and hypotension. But IT meperidine in a lower dose compared to IV one can decrease intensity and incidence of shivering and does not cause these side effects [21] [22].

In our study, like the study of Davoudi *et al.* [23] found that IT meperidine did not have any side effect.

Meperidine is composed of κ - and μ -receptor agonist. In comparison with μ -opioid agonists such as fentanyl, sufentanil, and morphine, IV meperidine is very more effective for shivering treatment. [24] Meperidine effect on shivering is related to non- μ -opioid receptors and more to κ -receptors. Because meperidine has activity in κ -receptors, correlation between anti-shivering effect of meperidine, and agonist activity of κ -receptor has been suggested in many studies. [24] [25].

As regard our study we can conclude that IT meperidine and IV meperidine are effective in controlling the postoperative shivering after spinal anesthesia in knee arthroscopic surgeries and there no significant difference between both root of admissions.

We agree with Zahid *et al.*, [26] who study Antishivering effects of two different doses of intrathecal meperidine in caesarean section and conclude that IT meperidine has a good effect on preventing the postoperative shivering.

Also agree with Shoaleh *et al.*, [27] who study the Effect of low dose of intrathecal pethidine on the incidence and intensity of shivering during cesarean section under spinal anesthesia approved that Low dose of intrathecal pethidine is safe, and can decrease the incidence and intensity of shivering during cesarean section, without having major side effects.

Ali Solhpour *et al.*, [28] concluded that Prophylactic use of meperidine is effective in preventing shivering resulting from spinal anesthesia.

Our study also agrees with Yu-Cih Lin *et al.*, [29] who approved that adjuvant low dose intrathecal meperidine effectively attenuates spinal anaesthesia-associated shivering and reduces rescue analgesics with residual concerns for the nausea and vomiting.

Also agree with Molouk *et al.*, [30] who study The Effect of Intrathecal Meperidine on Maternal and Newborn Outcomes after Cesarean Section and approved that Intrathecal meperidine can reduce shivering and increase the duration of postoperative analgesia.

Casey *et al.*, who study the Intravenous meperidine for control of shivering during caesarean section under epidural anesthesia.

Approved that Administration of IV meperidine resulted in a significant decrease in both the overall incidence of shivering and severity of shivering.

Our study agrees with Yu-Cih Lin *et al.*, [31] who study the effect of low dose intrathecal meperidine on preventing shivering and concluded that adjuvant low dose intrathecal meperidine effectively attenuates spinal anesthesia-associated shivering and reduces rescue analgesics.

4. Conclusion

We concluded that IT meperidine and IV meperidine comparably can decrease intensity and incidence of shivering compared to control group as well as decrease the requirement for additional doses of meperidine for shivering control without any hemodynamic side effects. And intrathecal meperidine showed better postoperative pain control and less postoperative nausea and vomiting (PONV).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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