DOES PROPHYLACTIC *PER* ORAL WARM WATER INTAKE REDUCE INCIDENCE OF SHIVERING POST SPINAL ANESTHESIA?

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DOES PROPHYLACTIC *PER* ORAL WARM WATER INTAKE REDUCE INCIDENCE OF SHIVERING POST SPINAL ANESTHESIA?

ABSTRACT

Background: Shivering is a frequent complication following anaesthesia, with an incidence of between 40-60% and 36-55% following general and neuraxial anaesthesia respectively. Shivering following spinal anesthesia is associated with many adverse events. The pharmacological prevention for post spinal shivering is diverse and not standardized amongst anaesthetists and evidence based protocols has not been established. The objective of this study is to assess the impact of oral administration of warm water administered prophylactically on the incidence of shivering after spinal anesthesia for Caesarean section.

Methods: Pregnant women at term, undergoing low-risk elective and grade 3 emergency lower segment Caesarean section under spinal anesthesia were recruited into the study. They were randomly assigned to either to receive oral warm water after the delivery of the fetus or to receive routine care (pharmacological treatment). They were observed for shivering and graded according to *Crossley & Mahajan* grading if shivering develops.

Results: 152 patients were recruited in the study, 75 in intervention arm and 77 in control arm. The overall incidence of shivering was 48%. There was no significant difference in the incidence of shivering between the interventional and control arms (49% v. 46%, p=0.888). Of those developed shivering, the majority (48%) had grade 3 (moderate) shivering. Two out of the 75 in the interventional arm reported mild adverse events (nausea and vomiting), which resolved upon reassuring them.

Conclusion: There was no significant difference in shivering among those who received oral warm water as a prophylaxis against shivering compared to the standard care (monitoring and pharmacological treatment if shivering develops).

ADAKAH MEMINUM AIR SUAM DAPAT MENGURANGKAN INSIDEN KEGIGILAN SELEPAS BIUS SEPARA BADAN?

ABSTRAK

Latar belakang: Kegigilan adalah komplikasi yang kerap berlaku berikutan bius, dengan kejadian di antara 40-60% dan 36-55% berikutan anestesia umum dan separuh badan masing-masing. Kegigilan berikutan bius dikaitkan dengan pelbagai komplikasi. Walaupun ada banyak teori dan kajian dilakukan, namun tiada pendapat yang jelas berkaitan dengan rawatan berkesan untuk mengurangkan gigilan disebabkan oleh bius. Objektif kajian ini adalah untuk mengkaji keberkesanan air suam dalam mengurangkan kadar gigilan selepas bius separa badan di antara wanita mengandung yang menjalani pembedahan *Caesarean section.*

Kaedah: Wanita hamil yang menjalani pembedahan *Caesarean section* berisiko rendah secara elektif atau kecemasan di bawah bius separa badan dimasukkan ke dalam kajian ini. Mereka secara rawak dibahagikan sama ada untuk menerima air suam selepas bayi dilahirkan atau untuk menerima rawatan rutin (rawatan farmakologi). Mereka diperhatikan sama ada kegigilan berlaku dan dinilai mengikut gred *Crossley & Mahajan* jika menggigil.

Keputusan: Seramai 152 pesakit disertakan di dalam kajian ini, 75 di dalam lengan *intervensi* dan 77 dalam lengan kawalan. Kadar keseluruhan menggigil ialah 48%. Tidak ada perbezaan yang ketara dalam kejadian menggigil di antara lengan intervensi dan lengan kawalan (49% v 46%, p=0.888). Daripada mereka yang menggigil, majoriti (48%) mengalami gred 3 (sederhana) gigilan. Dua dari 75 dalam lengan intervensi melaporkan kejadian buruk (mual dan muntah),dan hanya memerlukan sokongan.

Kesimpulan: Tidak ada perbezaan yang ketara dalam kadar gigilan di kalangan mereka yang menerima air suam sebagai pencegahan bila dibandingkan dengan rawatan rutin (pemantauan dan rawatan farmakologi jika menggigil).

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CHAPTER 1 : INTRODUCTION

Shivering is an involuntary, spontaneous, oscillatory mechanical activity of skeletal muscle associated with increased oxygen consumption[1]. It is meant to be a protective reflex that increases the production of body heat through muscle contraction and the body's next step in heat preservation after peripheral vasoconstriction[2].

Shivering is a frequent complication following surgery and anaesthesia, with an incidence of between 40-60% and 36-55% following general and neuraxial anaesthesia respectively[3][4]. The overall incidence of shivering following anaesthesia in a recent meta-analysis was 34%[5]. Shivering, along with pain, nausea and vomiting are causes of discomfort and dissatisfaction in patients undergoing Caesarean section . It can manifest in many grades, from a mild form of skin eruptions to a severe form with generalized continuous skeletal muscle contractions[6]. Patients report that shivering is remarkably uncomfortable, and some even find it worse than surgical pain[2]. Post spinal anesthesia shivering causes increase in postoperative pain via wound stretching, sympathetic stimulation, metabolic oxygen demand, lactic acidosis and carbon dioxide production. As a result, it causes increased stress on the cardiopulmonary system, via increases in cardiac output and minute ventilation, which can be detrimental in patients with limited reserves. Shivering also has implications on anesthetists as it interferes with monitoring devices such as the electrocardiogram (ECG), blood pressure cuffs and oxygen saturation monitor[7,8,9].

Shivering is usually triggered by hypothermia. However, it occurs even in normothermic patients during the perioperative period[10]. Exact causes of post spinal

shivering are still unclear though various mechanisms have been postulated. It may involve a combination of mechanisms, including modulation of thermoregulatory thresholds, changes in body heat distribution, reduction in body core temperature, and the cooling effect of the fluids injected into the neuraxis[11,12].

The most promising postulation is that, post anaesthesia shivering is predominantly thermoregulatory in nature as a result of the anaesthetic induced inhibition of thermal defense mechanisms and subsequent hypothermia[13,14]. Similar mechanisms surround neuraxial anaesthesia with the initial decrease in core body temperature being due to internal heat redistribution due to vasodilatation (Phase 1). Failure of vasoconstriction below the level of the blockade promotes ongoing heat loss (Phase 2)[15]. This also results in a lack of perception of cold in patients who routinely do not have intraoperative temperature monitoring when under neuraxial blockade. This further increases the risk of hypothermia which generally goes undetected in this subgroup of patients until shivering eventually manifests[16].

As shivering is poorly understood, the gold standard for its treatment has not been defined. Perioperative hypothermia prevention has been shown to be efficacious in avoiding shivering[17]. On the contrary, therapeutic strategies to manage shivering are mostly empirical. Two main strategies are available: pharmacological and non-pharmacological anti-shivering methods. The combination of forced-air warming devices and intravenous pethidine is the most validated method[18]. Many studies and meta-analyses analysed different medications; however, lack of sufficiently high-quality evidence has made it difficult for conclusions to be made about their comparative efficacies, and these commonly used medications (primarily opioids such as pethidine

and tramadol) are associated with undesirable side effects such as nausea, vomiting and drowsiness[19].

Previously, we have observed that patients undergoing lower segment Caesarean section under central neuraxial block are more likely to have their shivering terminated in the recovery area if they receive oral warm water, especially patients with full protective airway reflexes post regional anaesthesia (neuraxial and peripheral nerve blocks). Most patients feel comfortable and there was an observable reduction in the severity of shivering[6]. We hypothesize that warm water induces a rise in core temperature in gastrointestinal tract. As warm water had previously been shown to be efficacious, this study aimed to explore whether the prophylactic administration of warm water had any effects on the incidence and/or severity of shivering after spinal anesthesia following Caesarean section.

Research Objectives

Primary objective

To determine efficacy of per oral warm water in reducing post spinal shivering, as judged by:

1. Incidence of shivering in subjects receiving warm water vs routine care
2. Reduction of severity of shivering (as per *Crossley and Mahaja*n scale of shivering)

Secondary objectives

1. To determine the adverse events from intervention i.e incidence of nausea, vomiting

CHAPTER 2: LITERATURE REVIEW

Many studies have investigated the mechanism behind post anesthetic shivering, its consequences, various preventative and treatment modalities including the science behind each of these entities. Many therapeutic strategies exist for its treatment and most are empirical. Unfortunately, the overall quality of the antishivering guidelines is poor. Published analyses have not sufficiently demonstrated the efficacy of individual pharmacological and physical treatment options, and only a few studies of combination anti-shivering therapy exist[19].

Shivering in the post-anaesthetic care area can be rather brief. The American Society of Anesthesiologists (ASA) guidelines recommend forced-air warming devices and pethidine as the most highly validated method of preventing shivering[20]. As an overall, there are two main strategies: pharmacological and non-pharmacological anti-shivering methods.

To date, there is no published study/data on oral warm water as method of reducing perioperative shivering in the extensive literature review.

Non-pharmacological therapy

Active and passive warming were utilized in the shivering management in the perioperative period. Active warming, which includes forced air warming, intravenous fluid warming and heated mattresses, has shown more effectiveness at reducing temperature decline than passive warming, which revolves around the use of warmed cotton blankets or reflective coverings (Moola & Lockwood, 2011; NCCNSC 2008)[21].

Park et al.[22] found that active cutaneous warming was associated with the highest prevalence of positive outcomes in the clinical settings of patients undergoing surgery or induced hypothermia. There was agreement between these results and the current American Society of Anesthesiologists Task Force on Postanesthetic Care guidelines, which recommend forced-air warming, a common method of active cutaneous warming, to reduce shivering in the perioperative setting[20]. Horn et al. found perioperative forced-air warming of women undergoing Caesarean delivery while on epidural anesthesia prevented maternal and fetal hypothermia, reduced maternal shivering, and improved umbilical vein pH[23].

The combined application of heated intravenous fluids and forced-air warming had been shown to minimize core temperature loss. The latter method warmed the patient from outside in, whereas the former prevented a decrease in body temperature in the setting of redistribution hypothermia[24]. However, warmed fluids limit convective heat loss only when large quantities are infused, which may explain the limited effectiveness of this method. In contrast, a number of studies have found that warmed intravenous fluid as a single modality is effective in minimizing perioperative hypothermia. Five studies (Chung, et al., 2012; Goyal, et al., 2011; Oshvandi, et al., 2011; Smith, et al., 2000; Woolnough, Allam, et al., 2009) comparing IV fluid warming with room temperature fluids were combined in a meta-analysis on effectiveness of warmed IV fluids on the incidence of shivering. The combined result significantly favours intravenous fluid warming (OR 0.54, 95% CI 0.33-0.89) for reducing shivering in this population[25,26,27].

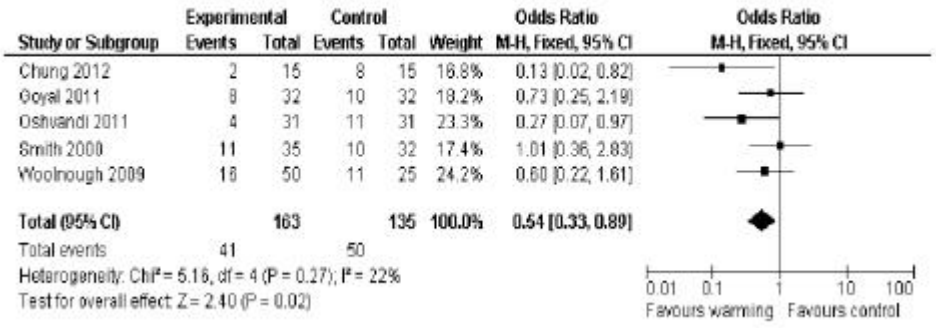


Figure 2.1: Intravenous fluid warming versus room temperature fluids and the incidence of shivering

Self et al. found that infusing intravenous fluids warmed to body temperature was associated with improved comfort compared to standard room temperature intravenous fluids but found no reduction in shivering in non perioperative setting[28].

Pharmacological therapy

The mechanism behind post spinal shivering is heterogenous, thus no single class of drug has been found to be the 'gold standard'. Many drugs have been shown to be effective on the prevention and treatment of shivering, such as opioids, α2-agonists, anticholinergics, central nervous system stimulants, corticosteroids. These drugs can be administered via various routes in the perioperative setting (intravenous, intramuscular, intrathecal, epidural).

Highly effective antishivering medication classes were centrally acting analgesics (tramadol), opioid receptor agonists (pethidine, fentanyl), cholinesterase inhibitors (physostigmine), and N-methyl-D-aspartate receptor antagonists (ketamine, magnesium sulfate). Meanwhile, α2-central agonists (clonidine, dexmedetomidine), and antiserotonergic (ondansetron) and anti-inflammatory drugs (dexamethasone) were

relatively less effective classes. This data support that medications which interfere at different levels of the thermoregulatory loop have more efficacy (opioid agonist, NMDA antagonist) than those with only one function (α2-receptor agonist, antiserotonergic agents) or only at the peripheral level (nonsteroidal anti-inflammatory agents).

Park et al. in a recent meta-analysis of all randomized, double-blinded, placebo controlled antishivering medications trials identified that clonidine, pethidine, tramadol, nefopam (a centrally acting nonopioid analgesic) and ketamine were the best performing pharmacological agents[5].

However, the adverse effects of medications limit their utility in many clinical settings. For example, pethidine and tramadol were associated with nausea, vomiting, drowsiness and neonatal respiratory depression[18,29,30,31].

CHAPTER 3: METHODS

Approval from the University of Malaya Medical Center's Institutional Review Board (Reference number: 20171025-5703) was obtained before embarking on the study. This is an Interventional, Prospective, Randomized, Controlled Trial. Pregnant women at term, with American Society of Anesthesiologist (ASA) physical status of I and II, undergoing low-risk elective and Grade 3 emergency lower segment Caesarean section under spinal anesthesia in University Malaya Medical Centre, Federal territory, Malaysia were recruited in this study.

The exclusion criteria were patients planned for Caesarean section under general anesthesia or those with potentially needing conversion to GA intraoperatively, obese (BMI $\geqq$40), febrile and underlying hypo/hyperthyroidism. Patients with more than 2 previous scars and history of failed/difficult spinal anesthesia were also excluded.

All patients were assigned randomly into two groups in a 1:1 ratio

1. Warm water group (A)
2. Standard care / control group (B)

Patients were invited to participate in the study immediately before anaesthesia for Caesarean section based on inclusion and exclusion criteria. Explanation and consent were taken by anaesthetist in the operation theater. Allocation schedule was obtained from an internet random number generator.

Patients were monitored by pulse oximetry, electrocardiogram (ECG) and noninvasive blood pressure every three minutes, and venous access obtained in the

upper limb with a 18G/20G catheter. Patients received 500 mL intravenous fluid at room temperature as co-infusion during the blockade. Patients' temperature was measured by a tympanic membrane thermometer.

With the patient in the sitting position, spinal anesthesia was performed with standard technique. Subsequently, patients were placed in the supine position with lateral deviation of the uterus to the left by tilting the operation table to the left. According to the institution routine, all patients had bladder catheterization. After assessing the satisfactory level of neuraxial blockade, lower segment Caesarean section was allowed to be performed with Pfannenstiel incision. Once the baby is delivered and patient remains pain free, those subjects randomized into Group A, 50-100ml of lukewarm water between 50-60°C was offered to the study subject per orally. Standard care was provided to those randomized into Group B. Standard care is defined as preventive measures such as active and passive warming, and pharmacological treatment (intravenous pethidine) once shivering develops (grade 3 and 4).

Vital signs (BP, Hr, Spo2) were charted every 5 minutes. Subjects were assessed for shivering. The onset and severity thereafter were recorded as per scale proposed by *Crossley & Mahajan* and modified grading. Routine care (pharmacological) with intravenous pethidine 25-50mg was administered to any subjects (of both groups) who developed shivering of grade 3 or more (rescue therapy). Postoperatively, patients were monitored as per standard care in the PACU. Incidence of nausea and vomiting were also recorded.

Anaesthetic Protocol

This standardized protocol was applied to both group of patients.

All patients were adequately fasted prior to surgery. Induction of anaesthesia was carried out with standard dose of intrathecal LA + fentanyl as decided by the performing anesthetist. Patients were monitored by ECG, $Sp0_2$, and non-invasive blood pressure. Core temperature via tympanic membrane thermometer monitored pre induction, at onset of shivering and in PACU. All patients received forced air warmer. No adjustment of the operating room temperature was made. The OT temperature prevailing at the time of the Caesarean section was recorded for each patients. All patients were monitored in PACU as per protocol.

Sample size determination:

To determine sample size for this study, we used power study. To prove the sample size adequacy for a study, this is a very useful and frequently used tool in medical research. The incidence of shivering post spinal anesthesia has been reported between 30-50% (mean 40%). The objective of this study is to see if warm water intake can reduce the incidence by 10%. To obtain an appropriate sample size from this population, we use the following formula. (https://www.stat.ubc.ca/~rollin/stats/ssize/b1.html)

$$N = \frac{p_0 q_0 \left\{ z_{1-\alpha/2} + z_{1-\beta} \sqrt{\frac{p_1 q_1}{p_0 q_0}} \right\}^2}{(p_1 - p_0)^2}$$

$$q_0 = 1 - p_0$$

$$q_1 = 1 - p_1$$

$$N = \frac{0.4 * 0.6 \left\{ 1.96 + 0.84 \sqrt{\frac{0.3*0.7}{0.4*0.6}} \right\}^2}{(0.3 - 0.4)^2}$$

$$N = 181$$

p_0 = proportion (incidence) of population
p_1 = proportion (incidence) of study group
N = sample size for study group
α = probability of type I error (usually 0.05)
β = probability of type II error (usually 0.2)
z = critical Z value for a given α or β

Considering 80% power of test, 5% marginal error and 10% reduction in incidence of shivering, the formula gave us a sample size of 181. In practice we had to enrol more participants to account for potential missing sample or level errors (Sakpal, 2010).

The formula of adjustment sample size is:

$n_1 = n/(1-d)$

n = required sample size as per formula

n_1 = is adjusted sample size

d = potential missing sample or level errors

Considering 20 percent potential missing sample or level errors, the adjusted sample size is 226. This is the minimum sample size we calculated; finally, our targeted sample size for this study was 230.

However, due to time constraints the final number of recruits were 152.

STATISTICAL ANALYSIS METHOD

Data obtained from this investigation was analysed using SPSS version 25.0. Descriptive statistics was used to evaluate the distribution, normality and homogeneity of the data. The Repeated Measures ANOVA was applied to determine if there were any significant difference/reduction of severity of shivering between the intervention and control arms. Any mean difference shown was considered significant if p-value showed less than 0.05. The chi square test was used to determine the association between the groups and grading score.

CHAPTER 4: RESULTS

Basic Demographics

Of a total of 152 patients, 77 (51%) were recruited in the control arm and 75 others (49%) in the interventional arm. All of them were females, with average age of 32.9. The patients' average height was 157.7 ± 15.5 cm, while their weight was 76.2 ± 12.2 kg. The patient's BMI was 32.7 ± 27.3 kgm^2, fulfilling inclusion criteria. All the subjects were of ASA 2 status, as they all had uncomplicated pregnancies. 85 (56%) of the subjects were Malay, 31 (21%) from Chinese race and Indians numbered at 20 (13%). The remaining 16 (10%) made up by foreigners. Out of the 172 patients, majority underwent elective lower segment Caesarean section (133; 87.5%), while the remaining grade 3 emergency lower segment Caesarean section (19; 12.5%).

The average ambient operating theatre (OT) temperature was 18.8℃. Baseline tympanic membrane temperature of patients upon arrival to OT was 36.2℃. The average tympanic membrane temperature among patients in interventional and control group did not differ much (35.8 ± 0.6 v. 35.6 ± 0.6). The average volume of the consumed warm water was 51.7 ± 9.2 ml, while the temperature of the water was 52.8 ± 4.2 ℃.

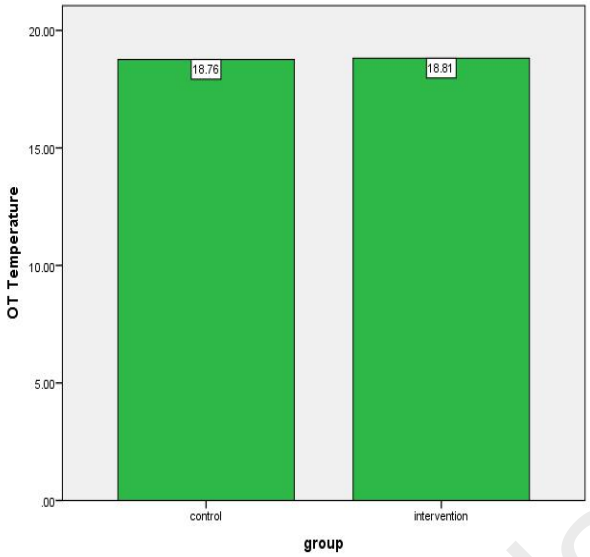


Figure 4.1: OT temperature

TABLE 4.1: Sociodemographic characteristics of patients (n=152)

Variable	Group		Whole group
	Control	Intervention	
Age	32.7 ± 4.0	33.2 ± 3.9	32.9 ± 3.9
Weight	76.4 ± 11.3	75.5 ± 12.7	76.2 ± 12.2
Height	158.4 ± 17.1	156.8 ± 13.7	157.7 ± 15.5
BMI	31.1 ± 8.4	34.4 ± 38.2	32.7 ± 27.3
Race			
Malay	42 (49.4)	43 (50.6)	85 (55.9)
Chinese	18 (58.1)	13 (41.9)	31 (20.5)
India	11 (55.0)	9 (45.0)	20 (13.1)
Others	6 (37.5)	10 (62.5)	16 (10.5)
Gender			
Male	0 (0.0)	0 (0.0)	0 (0.0)
Female	77 (51.0)	75 (49.0)	152 (100.0)
ASA			
I	0 (0.0)	0 (0.0)	0 (0.0)
II	77 (51.0)	75 (49.0)	152 (100.0)
III and above	0 (0.0)	0 (0.0)	0 (0.0)
Surgical procedure			
Grade 3 emergency LSCS	8 (42.1)	11 (57.9)	19 (12.5)
Elective LSCS	69 (51.9)	64 (48.1)	133 (87.5)
OT temperature	18.8 ± 1.4	18.7 ± 1.4	18.8 ± 1.4
Patients' temperature (baseline)	36.3 ± 0.6	36.2 ± 0.6	36.2 ± 0.6
Patients' temperature (intra & post op)	35.8 ± 0.6	35.6 ± 0.6	35.7 ± 0.6

TABLE 4.1: Sociodemographic characteristics of patients (n=152), continued

Previous history of perioperative shivering			
Yes	32 (51.6)	30 (48.4)	62 (40.7)
No	45 (50.1)	44 (49.4)	89 (58.9)
Anesthesia mode			
SAB/Epidural	29 (52.7)	26 (47.3)	55 (88.7)
GA	1 (25.0)	3 (75.0)	4 (6.5)
Regional	2 (66.7)	1 (33.3)	3 (4.8)

62 of the patients recruited (40.7%) had a history of perioperative shivering in the past. The majority (88.7%), had received neuraxial blockade (spinal or epidural) while the remaining had general anaesthesia (6.5%) or regional anaesthesic blockade (4.8%).

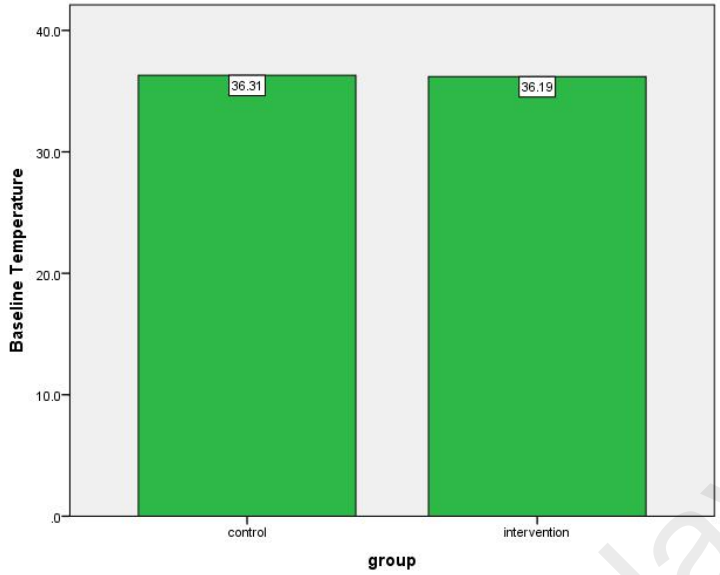


Figure 4.2: Baseline tympanic membrane temperature (℃) on arrival to OT

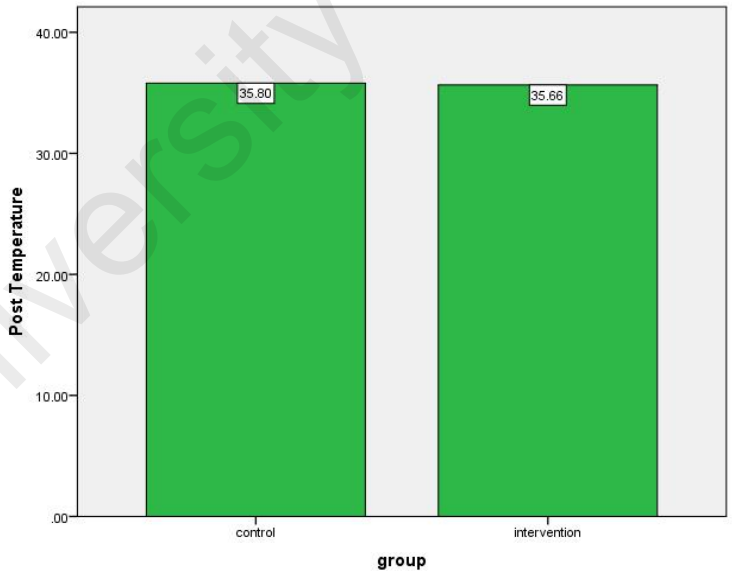


Figure 4.3: Average Intra-operative & PACU tympanic membrane temperature (℃)

Incidence of shivering in subjects between intervention and control group

Table 2 below shows the distribution of the patients based on the grading score. The majority of the patients experienced no shivering during operation and PACU. Based on the chi square test, there was no significant association between groups and grading score during operation (p=0.704), PACU (p=0.404) and both operation and PACU (p=0.888)

Table 4.2: Incidence of shivering according to *Crossley & Mahajan* grading

	Highest grading score	Frequency (%)		p value
		Control	Intervention	
Operation	0	43(55.8)	46(61.3)	0.704
	1	8(10.4)	4(5.3)	
	2	10(13.0)	7(9.3)	
	3	14(18.2)	15(20.0)	
	4	2(2.6)	3(4.0)	
PACU	0	50(64.9)	51(68.0)	0.404
	1	4(5.2)	9(12.0)	
	2	12(15.6)	8(10.7)	
	3	8(10.4)	6(8.0)	
	4	0(0.0)	1(1.3)	
	Unknown	3(3.9)	0(0.0)	
Overall (Operation+PACU)	0	41(53.2)	38(50.7)	0.888
	1	6(7.8)	7(9.3)	
	2	9(11.7)	10(13.3)	
	3	19(24.7)	16(21.3)	
	4	2(2.6)	4(5.3)	

Overall, the incidence of shivering in control group was 46% with majority of them (52%) having moderate grading (grade 3 according to *Crossley & Mahajan*). In the interventional group, the incidence of shivering is 49%, with 43% of these participants experiencing moderate shivering. Severe shivering was experienced by 2 (2.6%) in control group and 4 (5.3%) in interventional group.

More patients shivered in operation room (OR) than in the post anesthetic care unit (PACU) - 63 (41%) vs 51 (33%) explained by the colder OR temperature compared to the PACU temperature (18.8 v. 24°C).

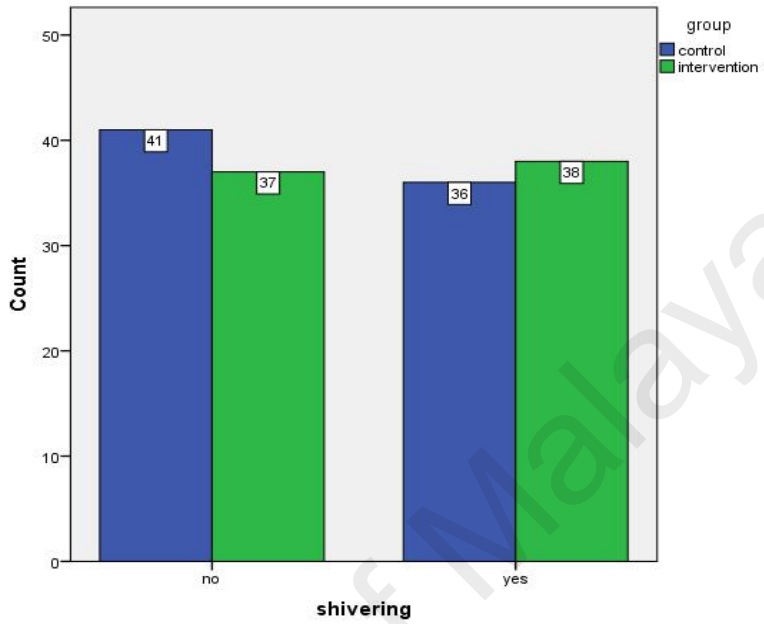
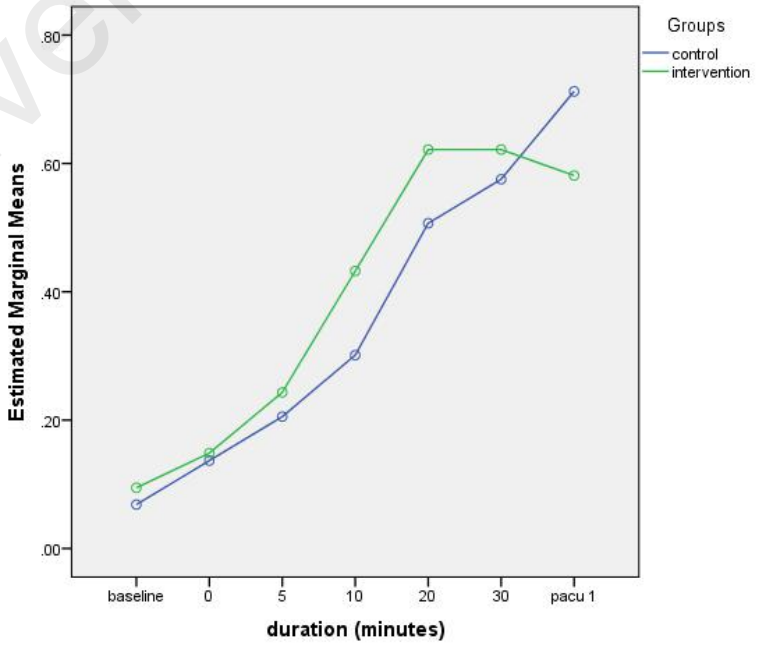


Figure 4.4: Overall incidence of shivering in absolute numbers

The graph below illustrates the mean response for each time interval based on groups.



Incidence of the adverse events from intervention

Two patients reported adverse events following the intervention, where one had nausea and another vomited. No further treatment needed to be administered to those who developed adverse events other than reassurance.

Rescue therapy

Table 4.3: Subjects requiring rescue therapy

	Control	Intervention	Overall
Yes	5 (83.3)	1 (16.7)	6 (4.1)
No	68 (47.9)	74 (52.1)	142 (95.9)

Six patients out of the 152 subjects (3.9%) required rescue therapy in the form of intravenous pethidine 25mg for moderate to severe shivering. More patients from the control group required rescue therapy compared to interventional group, 5 (83%) vs 1 (16.7%) respectively [p = 0.114].

CHAPTER 5 : DISCUSSION

To date, this is the first study exploring the use of prophylactic per oral warm water as a means to reduce shivering frequency and severity among patients undergoing lower segment Caesarean section under spinal anesthesia.

In our study, the overall incidence of shivering post spinal anaesthesia was 48%. This is within the reported incidence of 36-55% in the literature review[3,4]. This is a significantly high number, signifying more well-designed studies are needed to find solutions to overcome this relatively common problem in anesthesia.

In our study comparing oral warm water vs routine care, there was no significant difference in incidence of shivering (p value 0.888). However, the study sample is small compared to the initial target of 230 (80% power of test, 5% marginal error and 10% reduction in incidence of shivering).

There was no significant difference in perioperative tympanic membrane temperature and severity of shivering between both groups. The average intra-operative tympanic membrane temperature was 35.7 ± 0.6. This shows that the etiology of post anesthetic shivering is multifactorial, and hypothermia is not the only cause as shown in previous studies[10,11,12]. More patients shivered in operation room (OR) than in the post-anaesthetic care unit (41% v. 33%) which could be explained by lower OR temperature (18.8°C) and also patients were more exposed to heat loss from surgical site.

Despite less patients requiring rescue therapy in the form of IV Pethidine 25mg for moderate to severe shivering in the interventional arm compared to control arm, this is not statistically significant (p value 0.114 by fisher's exact test).

Only 2 out of the 75 subjects in the interventional arm (2.7%) who received oral warm water for prophylaxis against shivering, reported adverse events. 1 patient complained of nausea and another patient developed vomiting. Fortunately, both these events were mild in nature and only required reassurance.

As a conclusion, administration of oral warm water prophylactically has not been shown to significantly reduce frequency and/or severity of shivering.

One of the strengths of our study was the use of a novel intervention. However, the study also had some limitations:

- Larger sample size is required. The limited number in our study may have been responsible for the absence of difference between the 2 groups of patients.
- Whilst this study intended to use per oral warm water as a prophylactic measure before commencing surgery to reduce frequency and/or severity of post spinal shivering, however due to fear among anesthetist on the risk of aspiration in the event of conversion to general anesthesia is required intra-operatively, this has led to oral warm water being administered as a therapeutic measure once shivering developed rather than a prophylactic measure.

In the future, we may consider:

- Repeating the study with larger sample size
- Exploring the possibility of administering warm water in multiple doses as single dose has shown to be not effective according to this study (I.e. prior to wheeling patient to OT, after performing spinal anesthesia and after delivery of fetus).
- Conducting similar study on low risk non-obstetric patients undergoing surgeries under neuraxial or peripheral nerve blocks (I.e orthopedic, urology).

CHAPTER 6 : CONCLUSION

Shivering is a common complication post anesthesia with the incidence reported between 40-60%. It is thoroughly discomforting and has multitude of adverse effects on patients recovering from surgery and anesthesia. Effective prevention and treatment of shivering has become an essential step in increasing postoperative comfort and reducing shivering related complications. Management of post-anesthetic shivering can be pharmacological and non-pharmacological. However, they are not standardized amongst anaesthetists and evidence-based protocols has not been established.

We have studied the impact of warm water given orally in reduction of shivering. This is because warm water is readily available, cheap, easy to administer, non-invasive and can have psychological impact on patient as they are allowed to resume oral intake. However, this study has demonstrated that administration of per oral warm water has not been able to reduce the frequency and/or severity of shivering among low risk parturients undergoing lower segment Caeserean section under spinal anaesthesia.

However, to be consistent with the most up-to-date, evidence-based practice, we suggest that randomized controlled trials with larger number of subjects are needed to further investigate the safety and efficacy of orally administered warm water as a treatment rather than prophylaxis in reduction of post anesthetic shivering.

APPENDICES

APPENDIX A

DATA COLLECTION SHEET

Subject Number:

PATIENT INFORMATION

Name	*Paste patients' sticker here*
R/N	
Age	
Race	Malay / Chinese / Indian / Others
Gender	Male / Female
ASA	I or II
Weight (kg)	
Height (cm)	
BMI	
Diagnosis	
Surgical Procedure	Emergency/Elective LSCS

Previous history of peri-operative shivering: Yes/No

If **Yes**, Surgery: _____ Mode of anesthesia: _____

Preoperative tympanic membrane temperature: _____ºC

Operating room ambient temperature: _____ ºC

1.	Time of patient transfer to operating theatre table	
2.	Time of spinal anesthesia	
3.	Time of surgical incision	
4.	Time of oral warm water administered (If randomized into Group A) & Total volume/Temperature of water	/ (ml)/ ºC
5.	Time of end of surgery	
6.	Time of patient transfer to post anesthetic care unit (PACU)	
7	Time discharge to ward	

Intra-operative Data

Time (min)	Baseline	0	5	10	20	30	40	50	60
SBP/DBP									
MAP									
HR (bpm)									
Temperature (°C)									
Grading of shivering* *Crossley & Mahajan (0 to4)*									
Modified grading (0 to 2)									

Time (min)	70	80	90	100	120	PACU	PACU	PACU	PACU
SBP/DBP									
MAP									
HR (bpm)									
Temperature (°C)									
Grading of shivering* *Crossley & Mahajan (0 to4)*									
Modified grading (0 to 2)									

0 = time spinal anesthesia performed

Time of onset of shivering: _____

Rescue drug for shivering: Yes / No

If Yes, type of drug & dose: _____

Side Effect of oral warm water: Yes / No

If Yes, indicate side effect

- Nausea Y/N, Treatment: _____
- Vomiting Y/N, Treatment: _____
- Aspiration Y/N, Treatment: _____

Patient satisfaction:

1	2	3	4	5	6	7	8	9	10

**Notes:*

GRADING OF SHIVERING

Crossley and *Mahajan* have graded the intensity of PAS using the following scale:

0 = no shivering;

1 = no visible muscle activity but piloerection, peripheral vasoconstriction, or both are present (other causes excluded);

2 = muscular activity in only one muscle group;

3 = moderate muscular activity in more than one muscle group but no generalized shaking;

4 = violent muscular activity that involves the whole body.

Modified grading

A scale more specific to neuraxial anaesthesia would incorporate

0 = no shivering

1 = shivering not interfering with monitoring or causing patient distress

2 = shivering interfering with monitoring or causing patient distress

APPENDIX B

UNIVERSITI MALAYA
KUALA LUMPUR

CONSENT BY PATIENT FOR CLINICAL RESEARCH VERSION 1 (25/10/2017)

I, ……Identity Card No……..……

(Name of Patient)

of …… *(Address)*

hereby agree to take part in the clinical research (clinical study/questionnaire study/drug trial) specified below:

Title of Study: *Does prophylactic per oral warm water intake reduce incidence of shivering post spinal anesthesia?*

the nature and purpose of which has been explained to me by Dr. ..……..……

(Name & Designation of Doctor)

and interpreted by ……..……..……

(Name & Designation of Interpreter)

…….. to the best of his/her ability in ……..…… language/dialect.

I have been told about the nature of the clinical research in terms of methodology, possible adverse effects and complications (as per patient information sheet). After knowing and understanding all the possible advantages and disadvantages of this clinical research, I voluntarily consent of my own free will to participate in the clinical research specified above.

I understand that I can withdraw from this clinical research at any time without assigning any reason whatsoever and in such a situation shall not be denied the benefits of usual treatment by the attending doctors.

Date: ……...…….. Signature or Thumbprint ……..……

(Patient)

IN THE PRESENCE OF

Name ……..…….…..…)

Identity Card No. ……..……) Signature

(*Witness for Signature of Patient)*

Designation ……..……)

I confirm that I have explained to the patient the nature and purpose of the above-mentioned clinical research.

Date ……. Signature ……

(Attending Doctor)

BK-MIS-1117-E02

CONSENT BY PATIENT FOR CLINICAL RESEARCH	R.N. Name Sex Age	*sticker*

APPENDIX C

KEIZINAN OLEH PESAKIT UNTUK PENYELIDIKAN KLINIKAL VERSI 1 (25/10/2017)

Saya,……(*Nama Pesakit),* No. Kad Pengenalan ……..…… bereralamat…… (*Alamat)*

dengan ini bersetuju menyertai dalam penyelidikan klinikal (pengajian klinikal/pengajian soal-selidik/percubaan ubat-ubatan) disebut berikut:

TajukPenyelidikan: *Adakah meminum air suam dapat mengurangkan insiden kegigilan selepas bius separa badan?*

yang mana sifat dan tujuannya telah diterangkan kepada saya oleh Dr.……

(Nama & Jawatan Doktor) mengikut terjemahan ……..…… *(Nama & Jawatan Penterjemah)* yang telah menterjemahkan kepada saya dengan sepenuh kemampuan dan kebolehannya di dalam Bahasa / loghat……

Saya telah diberitahu bahawa dasar penyelidikan klinikal dalam keadaan methodologi, risiko dan komplikasi (mengikut kertas maklumat pesakit). Selepas mengetahui dan memahami semua kemungkinan kebaikan dan keburukan penyelidikan klinikal ini, saya merelakan/mengizinkan sendiri menyertai penyelidikan klinikal tersebut di atas.

Saya faham bahawa saya boleh menarik diri dari penyelidikan klinikal ini pada bila-bila masa tanpa memberi sebarang alasan dalam situasi ini dan tidak akan dikecualikan dari kemudahan rawatan dari doktor yang merawat.

Tarikh: …….. Tandatangan/Cap Jari ……

(Pesakit)

DI HADAPAN

Nama ……)

No. K/P……) Tandatangan

(Saksi untuk Tandatangan Pesakit)

Jawatan ……..……)

Saya sahkan bahawa saya telah menerangkan kepada pesakit sifat dan tujuan penyelidikan klinikal tersebut di atas.

Tarikh: ……. Tandatangan ……

(Doktor yang merawat)

BK-MIS-1117-E02

KEIZINAN OLEH PESAKIT
UNTUK
PENYELIDIKAN KLINIKAL

No Pendaftaran
Nama
Jantina
Umur

pelekat

APPENDIX D

UNIVERSITY OF MALAYA MEDICAL CENTRE

PATIENT INFORMATION SHEET

Research Title:

Does prophylactic *per* oral warm water intake reduce incidence of shivering post spinal anesthesia?

We would like to invite you to take part in a research study. Before you decide whether to participate, you need to understand why the research is being done and what it would involve. Please take time to read the following information carefully; talk to others about the study if you wish.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Shivering is a frequent complication following anaesthesia. It is an unpleasant, thoroughly discomforting to patient. Post spinal anesthesia shivering is associated with significant complications which includes increase in postoperative pain, stress on cardiorespiratory system especially in patients with poor reserve and also imposes difficulty with monitoring techniques (ecg, bp, sp02). Although numerous theories and evidence based literature exist, there is no clear concensus with regards to the treatment of post anesthesia shivering. Textbooks have suggested numerous pharmacological interventions for the treatment of postoperative shivering but the relative efficacy of these drugs remains inconclusive and they are associated with many drug related side effects. We have observed that patient undergoing lower segment caesarean section under spinal anesthesia can have their shivering brought under control if they receive oral warm water. Thus, we would like study the impact of oral administration of warm water in reducing shivering post spinal anesthesia.

Why have I been invited?

All the patients who are scheduled for low risk elective and grade 3 emergency lower segment caesarean section under spinal anesthesia will be invited to take part in this study.

What would this involve?

If you agree to take part in this research study you will be randomly (like the tossing of a coin) assigned to receive one of the two treatments listed below.

After spinal anesthesia is administered to you, adequacy of the block for surgery will be assessed by your anesthetist and surgery will be allowed to proceed. Once the baby is delivered and you remain pain free, you will be either given warm water to drink if you are randomized into group 1 or monitored as per standard practise if randomized into group 2.

Group 1 = 150-200ml of warm water given orally

Group 2 = no intervention (control group)

We will monitor your vital signs (heart rate, blood pressure and oxygen saturation) and grade of shivering every 5 minutes until the end of surgery.

What are the possible benefits of taking part?

Taking part in this study will probably not directly benefit your care in hospital. Knowledge gained from this research may assist us in treating other patients in the future.

What are the possible risks of taking part?

Drinking warm water may induce nausea and vomiting. You will be administered drugs if develop those side effects.

If I do not want to take part in the study, are there other choices?

It is important for you to know that you can choose not to take part in the study. Choosing not to participate in this study will in no way affect your care or treatment.

Will there be any costs?

Your participation in this research project will not involve any additional costs to you or your health care insurer.

Will my taking part in the study be kept confidential?

Yes. The result of the data obtained will be reported in a collective manner with no reference to a specific individual. Hence, the data from each individual will remain confidential.

Who has reviewed the study?

The study has been reviewed and approved by the Medical Ethics Committee University Malaya Medical Centre.

If I have any questions, whom can I ask at any point of the study?

Dr James Joseph (Trainee)	Professor Chan Yoo Kuen (Supervisor)
Department of Anaesthesiology and Intensive Care, University Malaya Medical Centre (UMMC)	Department of Anaesthesiology and Intensive Care, University Malaya Medical Centre (UMMC)
Tel: 017-2710315	Tel: 03-79492052

APPENDIX E

UNIVERSITY OF MALAYA MEDICAL CENTRE

MAKLUMAT UNTUK PESAKIT

Tajuk Penyelidikan:

Adakah meminum air suam dapat mengurangkan insiden kegigilan selepas bius separa badan?

Kami ingin menjemput anda untuk mengambil bahagian dalam kajian penyelidikan. Sebelum anda membuat keputusan untuk mengambil bahagian, anda perlu memahami sebab penyelidikan yang sedang dilakukan dan apa yang kajian ini akan melibatkan. Sila luangkan masa untuk baca maklumat berikut dengan teliti; berbincang dengan orang lain mengenai kajian ini jika anda mahu.

Tanya kami jika ada apa-apa yang tidak jelas atau jika anda ingin maklumat lanjut. Ambil masa untuk membuat keputusan sama ada anda setuju untuk mengambil bahagian dalam kajian ini.

Apakah tujuan penyelidikan ini?

Gigilan adalah komplikasi yang kerap berlaku selepas bius. Ia adalah tidak menyelesakan kepada pesakit. Gigilan yang berlaku susulan bius separuh badan dikaitkan dengan pelbagai komplikasi seperti peningkatan kesakitan selepas pembedahan, tekanan pada sistem pernafasan dan kardiovascular terutamanya pada pesakit yang sudah pun ada masalah jantung and paru-paru dan ia juga menyukarkan teknik pemantauan pesakit(ecg, bp, sp02). Walaupun ada banyak teori dan kajian dilakukan, namun tiada konsensus yang jelas berkaitan dengan rawatan berkesan untuk mengurangkan gigilan disebabkan oleh bius. Buku teks telah mencadangkan pelbagai jenis ubat untuk rawatan mengurangkan gigilan, tetapi keberkesanan ubat-ubatan ini masih tiada bukti yag kukuh dan mereka dikaitkan dengan banyak kesan sampingan yang berkaitan dengan ubat-ubat tersebut. Kami telah memerhatikan bahawa pesakit yang menjalani pembedahan bersalin secara caesarean di bawah bius separa badan, gigilan dapat dikurangkan apabila pesakit diberi air suam untuk diminum. Oleh itu, kami ingin mengkaji keberkesaan air suam dalam megurangkan gigilan disebabkan oleh bius.

Mengapa saya diajak dalam penyelidikan ini?

Semua pesakit berisiko rendah yang dijadualkan untuk menjalani pembedahan caesarean secara elektif dan emergency gred 3 di bawah bius separa badan akan dijemput untuk mengambil bahagian dalam kajian ini.

Apa yang akan dilakukan?

Jika pesakit bersetuju untuk mengambil bahagian dalam penyelidikan ini, pesakit akan dibahagikan secara rawak (seperti melambung duit syiling) untuk menerima salah satu daripada dua rawatan yang disediakan di bawah.

Selepas bius separa badan diberikan kepada anda, tahap blok akan dinilai oleh pakar bius. Jika tahap bius adalah cukup, pembedahan akan dilakukan. Selepas bayi dilahirkan and anda masih lali disebabkan oleh bius, anda akan diberi air suam untuk diminum jika anda diundi ke kumpulan 1, dan akan diperhatikan seperti biasa dan rawatan rutin diberi jika diundi ke kumpulan 2.

Kumpulan 1: 150-200ml air suam untuk diminum

Kumpulan 2: Tiada intervensi (kumpulan control)

Kami akan memantau kadar jantung, tekanan darah dan oksigen serta gred menggigil setiap 5 minit sehingga akhir pembedahan.

Apakah manfaat mengambil bahagian dalam penyelidikan ini?

Mengambil bahagian dalam kajian ini mungkin tidak memberi manfaat kepada anda secara langsung. Pengetahuan yang diperoleh daripada penyelidikan ini boleh membantu kami dalam merawat pesakit lain pada masa akan datang.

Apakah risiko mengambi bahagian dalam penyelidikan ini?

Meminum air suam boleh menyebabkan mual dan muntah. Anda akan diberi ubat sekiranya kesan sampingan tersebut berlaku.

Perlukah saya mengambil bahagian?

Adalah penting bagi anda mengetahui bahawa anda boleh memilih untuk tidak mengambil bahagian dalam penyelidikan ini. Memilih untuk tidak mengambil bahagian dalam penyelidikan ini akan sama sekali tidak menjejaskan penjagaan atau rawatan anda.

Bayaran dan pampasan?

Penyertaan anda dalam projek penyelidikan ini tidak akan melibatkan apa-apa kos tambahan kepada anda atau syarikat insurans penjagaan kesihatan anda.

Penyertaan saya dalam kajian ini akan dirahsiakan?

Ya. Hasil daripada data yang diperolehi akan dilaporkan secara kolektif tanpa merujuk kepada individu tertentu. Oleh itu, data dari setiap individu akan kekal sulit.

Siapa yang telah mengkaji penyelidikan ini?

Penyelidikan ini telah diteliti dan diluluskan oleh Medical Ethnics Committee Pusat Perubatan Universiti Malaya.

Jika saya mempunyai sebarang pertanyaan, siapa saya boleh hubungi?

Dr James Joseph (Trainee)	Professor Chan Yoo Kuen (Supervisor)
Department of Anaesthesiology and Intensive Care, University Malaya Medical Centre (UMMC)	Department of Anaesthesiology and Intensive Care, University Malaya Medical Centre (UMMC)
Tel: 017-2710315	Tel: 03-79492052

APPENDIX F

GRADING OF SHIVERING

Crossley and *Mahajan* have graded the intensity of PAS using the following scale:

. 0 = no shivering;

1 = no visible muscle activity but piloerection, peripheral vasoconstriction, or both are present (other causes excluded);

2 = muscular activity in only one muscle group;

3 = moderate muscular activity in more than one muscle group but no generalized shaking;

4 = violent muscular activity that involves the whole body.

Modified grading

A scale more specific to neuraxial anaesthesia would incorporate

0 = no shivering

1 = shivering not interfering with monitoring or causing patient distress

2 = shivering interfering with monitoring or causing patient distress

REFERENCES

[1] Jan De Witte, Daniel I. Sessler; Perioperative Shivering: Physiology and Pharmacology. Anesthesiology 2002;96(2):467-84.

[2] Lopez MB. Postanaesthetic shivering - from pathophysiology to prevention. Rom J Anaesth Intensive Care. 2018;25(1):73-81.

[3] Horn E-P, Sessler DI, Standl T, et al. Non-thermoregulatory shivering in patients recovering from isoflurane or desflurane anesthesia, Anesthesiology 1998; 89: 878-86.

[4] Panzer O, Ghazanfari N, Sessler DI, et al. Shivering and shivering-like tremor during labour with and without epidural analgesia, Anesthesiology 1999; 90: 1609-16.

[5] Park SM, Mangat HS, Berger K, Rosengart AJ. Efficacy spectrum of antishivering medications: Meta-analysis of randomized controlled trials. Crit Care Med. 2012;40:3070–82. doi: 10.1097/CCM.0b013e31825b931e. [PubMed] [CrossRef].

[6] A. W. A. Crossley And R. P. Mahajan. The intensity of postoperative shivering is unrelated to axillary temperature.Anaesthesia, 1994, Volume 49, pages 205-207.

[7] Bhatnagar S, Saxena A, Kannan TR, Punj J, Panigrahi M, Mishra S. Tramadol for postoperative shivering: A double blind comparison with Pethedine. Anaesth Intensive care. 2001;29:149–54. [PubMed].

[8] Katyal S, Tewari A. Shivering: Anesthetic Considerations. J Anaesth Clin Pharmacol. 2002;18:363–76.

[9] Sessler Daniel I. Temperature Monitoring. In: Millar RD, editor. Textbook of Anaesthesia. 5th ed. New York: Churchill Livingstone Inc; 1994. pp. 1367–89.

[10] Eberhart LH, Döderlein F, Eisenhardt G, Kranke P, Sessler DI, Torossian A, et al. Independent risk factors for postoperative shivering. Anesth Analg. 2005;101:1849–1857. doi: 10.1213/01.ANE.0000184128.41795.FE. [PubMed] [CrossRef].

[11] Asami T, Hori T, Kiyohara T, Nakashima T. Convergence of thermal signals on the reticulospinal neurons in the midbrain, pons and medulla oblongata. Brain Res Bull. 1988;20:581–96. doi: 10.1016/0361-9230(88)90217-1. [PubMed] [CrossRef].

[12] Sessler DI, Rubinstein EH, Moayeri A. Physiologic responses to mild perianesthetic hypothermia in humans. Anesthesiology. 1991;75:594–610. [PubMed]

[13] POST ANAESTHESIA SHIVERING (PAS): A REVIEW Dr. Pradip K. Bhattacharya1 Dr. Lata Bhattacharya Dr. Rajnish K. Jain Dr. Ramesh C. Agarwal.Indian J. Anaesth. 2003; 47 (2) : 88-93.

[14] Frank SM, El-Rahmany HK, Cattaneo CG, Barnes RA. Predictors of hypothermia during spinal anesthesia. Anesthesiology. 2000;92:1330–4. [PubMed].

[15] Morgan GE, Mikhail MS, Murray MJ. Clinical Anaesthesiology fourth edition. 2006. 148-150.

[16] Frank SM, Nguyen JM, Garcia CM, Barnes RA. Temperature monitoring practices during regional anesthesia. Anesth Analg. 1999;88:373–7. [PubMed].

[17] Roberson MC, Dieckmann LS, Rodriguez RE, Austin PN. A review of the evidence for active preoperative warming of adults undergoing general anesthesia. AANA J. 2013;81:351–6. [PubMed].

[18] Dabir S, Jahandideh M, Abbasinazari M, Kouzekanani H, Parsa T, Radpay B. The efficacy of a single dose of pethidine, fentanyl and morphine in treating postanesthesia shivering. Pak J Pharm Sci. 2011;24:513–7. [PubMed].

[19] Choi KE, Park B, Moheet AM, Rosen A, Lahiri S, Rosengart A. Systematic Quality Assessment of Published Antishivering Protocols. Anesth Analg. 2017;124:1539–46. doi: 10.1213/ANE.0000000000001571.

[20] Practice Guidelines for Postanesthetic Care: An Updated Report by the American Society of Anesthesiologists Task Force on Postanesthetic Care. Updated by the Committee on Standards and Practice Parameters; Jeffrey L. Apfelbaum, M.D.; the Task Force on Postanesthetic Care; Jeffrey H. Silverstein, M.D.; Frances F. Chung, M.D.; et al. Anesthesiology 02 2013, Vol.118, 291-307. doi:10.1097/ ALN. 0b013e31827773e9.

[21] Moola, Sandeep & Lockwood, Craig. (2010). The effectiveness of strategies for the management and/or prevention of hypothermia within the adult perioperative environment: Systematic review. JBI Library of Systematic Reviews. 8. 752-92. 10.11124/01938924-201008190-00001.

[22] Park B, Lee T, Berger K, Park SM, Choi KE, Goodsell TM, et al. Efficacy of Nonpharmacological Antishivering Interventions: A Systematic Analysis. Crit Care Med. 2015;43:1757–66. doi: 10.1097/CCM.0000000000001014. [PubMed] [CrossRef].

[23] Horn EP, Schroeder F, Gottschalk A, et al. Active warming during cesarean delivery. Anesth Analg 2002; 94: 409–14.

[24] Cobb B, Cho Y, Hilton G, Ting V, Carvalho B. Active Warming Utilizing Combined IV Fluid and Forced-Air Warming Decreases Hypothermia and Improves Maternal Comfort During Cesarean Delivery: A Randomized Control Trial. Anesth Analg. 2016;122:1490–7. doi: 10.1213/ANE.0000000000001181.[PubMed] [CrossRef].

[25] Woolnough M, Allam J, Hemingway C, Cox M, Yentis SM. Intra-operative fluid warming in elective caesarean section: a blinded randomised controlled trial. Int J Obstet Anesth. 2009;18:346–51. doi: 10.1016/j.ijoa.2009.02.009. [PubMed] [CrossRef].

[26] Goyal P, Kundra S, Sharma S, Grewal A, Kaul TK, Singh MR. Efficacy of intravenous fluid warming for maintenance of core temperature during lower segment cesarean section under spinal anesthesia. J Obstet Anaesth Crit Care. 2011;1:73–7. doi: 10.4103/2249-4472.93990. [CrossRef].

[27] Chung SH, Lee BS, Yang HJ, Kweon KS, Kim HH, Song J, et al. Effect of preoperative warming during cesarean section under spinal anesthesia. Korean J Anesthesiol. 2012;62:454–60. doi: 10.4097/kjae.2012.62.5.454. [PMC free article] [PubMed] [CrossRef].

[28] Self, Wesley & J White, Steven & Mcnaughton, Candace & B Storrow, Alan & M Slovis, Corey & P Collins, Sean. (2013). Warming Intravenous Fluids for Improved Patient Comfort in the Emergency Department: A Pilot Crossover Randomized Controlled Trial. The western journal of emergency medicine. 14. 542-6. 10.5811/westjem.2013.1.13303.

[29] Lin YC, Chen CY, Liao YM, Liao AH, Lin PC, Chang CC. Preventing shivering with adjuvant low dose intrathecal meperidine: A meta-analysis of randomized

controlled trials with trial sequential analysis. Sci Rep. 2017;7:15323. doi: 10.1038/s41598-017-14917-5. [PMC free article] [PubMed] [CrossRef].

[30] Zhou C, Zhu Y, Liu Z, Ruan L. 5-HT3 receptor antagonists for the prevention of postoperative shivering: a meta-analysis. J Int Med Res. 2016;44:1174–81. doi: 10.1177/0300060516668776.[PMC free article] [PubMed] [CrossRef].

[31] Kranke, Peter & H Eberhart, Leopold & Roewer, Norbert & R Tramèr, Martin. (2002). Pharmacological Treatment of Postoperative Shivering: A Quantitative Systematic Review of Randomized Controlled Trials. Anesthesia and analgesia. 94. 453-60, table of contents. 10.1097/00000539-200202000-00043.