Brunei International Medical Journal

OFFICIAL PUBLICATION OF THE MINISTRY OF HEALTH AND UNIVERSITI BRUNEI DARUSSALAM

Volume 17 20 April 2021 (8 Ramadhan 1442H)

A RANDOMISED CONTROLLED TRIAL COMPARING INTRATHECAL FENTANYL-MORPHINE-BUPIVACAINE VERSUS INTRATHECAL FENTANYL-BUPIVACAINE IN WOMEN UNDERGOING CESAREAN SECTION.

Sudhirchandra SHAH [1], Dhadappa Damodar SRIDHARAN[1], Iqbal HUSSAIN[1], Thomas Abraham JACOBS[1], Maebelle CAYOWET[1], Chee Fui CHONG[2].

[1]Department of Anaesthesia, Suri Seri Begawan Hospital, Kuala Belait, Brunei Darussalam.
[2]Clinical Research Unit, Raja Isteri Pengiran Anak Saleha Hospital, Bandar Seri Begawan, Brunei Darussalam.

ABSTRACT

Objective: Comparison of the effectiveness and duration of Intrathecal fentanyl-morphine-bupivacaine versus intrathecal fentanyl-bupivacaine for post-operative analgesia after cesarean section. **Material and Method:** A prospective single blinded randomized controlled trial comparing intrathecal fentanyl-morphine-bupivacaine versus intrathecal fentanyl-bupivacaine for post-operative pain relief in caesarean section was conducted. Fifty parturient women, ASA physical status 1 and 2, were randomized into two groups. Group A received fentanyl 15 µgm, morphine 100 µgm and bupivacaine 10 mg intrathecally and Group B received fentanyl 25 µgm and bupivacaine 10 mg intrathecally. The primary outcome was quality and duration of postoperative analgesia. Block characteristic, haemodynamic variables, demand for rescue analgesia and adverse effects were also assessed. Intention to treat analysis was performed at the end of the study. P<0.05 was considered as statistical significance. **Results:** The demographic profiles and block characteristics were comparable in both groups except women in Group A underwent more additional procedures besides caesarean section (*p=0.044)*. The mean total morphine requirement post-operatively for the first 24 hours in Group A was 8.73 +/- 7.39 mg and Group B was 14.95 +/- 5.86 mg respectively, which was statistically significant *(p=0.004)*. Mean VAS score was also significantly lower in Group A *9p=0.049)* as was the need for additional analgesia *(p=0.024).* There were two cases of pruritus in Group B and one case of vomiting in Group A. There were no cases of respiratory depression. Fetal APGAR scores were similar in both groups. **Conclusion:** The use of intrathecal fentanyl-morphine-bupivacaine combination resulted in a more effective and longer duration of post-operative analgesia as compare to intrathecal fentanyl-bupivacaine in parturient women undergoing cesarean section under spinal anaesthesia.

Key words: Analgesia, Bupivacaine, Cesarean section, Fentanyl, Morphine, Post-operative, Spinal anaesthesia.

Brunei Int Med J. *2021;17:45-54*

ISSN 1560 5876 Print
ISSN 2079 3146 Online

Online version of the journal is available at www.bimjonline.com

Brunei International Medical Journal (BIMJ)
Official Publication of
The Ministry of Health
and
Universiti Brunei Darussalam

ISSN 1560-5876 Print
ISSN 2079-3146 Online

Aim and Scope of Brunei International Medical Journal

The Brunei International Medical Journal (BIMJ) is a six monthly peer reviewed official publication of the Ministry of Health under the auspices of the Clinical Research Unit, Ministry of Health, Brunei Darussalam.

The BIMJ publishes articles ranging from original research papers, review articles, medical practice papers, special reports, audits, case reports, images of interest, education and technical/innovation papers, editorials, commentaries and letters to the Editor. Topics of interest include all subjects that relate to clinical practice and research in all branches of medicine, basic and clinical including topics related to allied health care fields. The BIMJ welcomes manuscripts from contributors, but usually solicits reviews articles and special reports. Proposals for review papers can be sent to the Managing Editor directly. Please refer to the contact information of the Editorial Office.

Instruction to authors

Manuscript submissions

All manuscripts should be sent to the Managing Editor, BIMJ, Ministry of Health, Brunei Darussalam; e-mail: editor-in-chief@bimjonline.com. Subsequent correspondence between the BIMJ and authors will, as far as possible via should be conducted via email quoting the reference number.

Conditions

Submission of an article for consideration for publication implies the transfer of the copyright from the authors to the BIMJ upon acceptance. The final decision of acceptance rests with the Editor-in-Chief. All accepted papers become the permanent property of the BIMJ and may not be published elsewhere without written permission from the BIMJ.

Ethics

Ethical considerations will be taken into account in the assessment of papers that have experimental investigations of human or animal subjects. Authors should state clearly in the Materials and Methods section of the manuscript that institutional review board has approved the project. Those investigators without such review boards should ensure that the principles outlined in the Declaration of Helsinki have been followed.

Manuscript categories

Original articles

These include controlled trials, interventional studies, studies of screening and diagnostic tests, outcome studies, cost-effectiveness analyses, and large-scale epidemiological studies. Manuscript should include the following; introduction, materials and methods, results and conclusion. The objective should be stated clearly in the introduction. The text should not exceed 2500 words and references not more than 30.

Review articles

These are, in general, invited papers, but unsolicited reviews, if of good quality, may be considered. Reviews are systematic critical assessments of literature and data sources pertaining to clinical topics, emphasising factors such as cause, diagnosis, prognosis, therapy, or prevention. Reviews should be made relevant to our local setting and preferably supported by local data. The text should not exceed 3000 words and references not more than 40.

Special Reports

This section usually consist of invited reports that have significant impact on healthcare practice and usually cover disease outbreaks, management guidelines or policy statement paper.

Audits

Audits of relevant topics generally follow the same format as original article and the text should not exceed 1,500 words and references not more than 20.

Case reports

Case reports should highlight interesting rare cases or provide good learning points. The text should not exceed 1000 words; the number of tables, figures, or both should not be more than two, and references should not be more than 15.

Education section

This section includes papers (i.e. how to interpret ECG or chest radiography) with particular aim of broadening knowledge or serve as revision materials. Papers will usually be invited but well written paper on relevant topics may be accepted. The text should not exceed 1500 words and should include not more than 15 figures illustration and references should not be more than 15.

Images of interest

These are papers presenting unique clinical encounters that are illustrated by photographs, radiographs, or other figures. Image of interest should include a brief description of the case and discussion with educational aspects. Alternatively, a mini quiz can be presented and answers will be posted in a different section of the publication. A maximum of

three relevant references should be included. Only images of high quality (at least 300dpi) will be acceptable.

Technical innovations
This section include papers looking at novel or new techniques that have been developed or introduced to the local setting. The text should not exceed 1000 words and should include not more than 10 figures illustration and references should not be more than 10.

Letters to the Editor
Letters discussing a recent article published in the BIMJ are welcome and should be sent to the Editorial Office by e-mail. The text should not exceed 250 words; have no more than one figure or table, and five references.

Criteria for manuscripts
Manuscripts submitted to the BIMJ should meet the following criteria: the content is original; the writing is clear; the study methods are appropriate; the data are valid; the conclusions are reasonable and supported by the data; the information is important; and the topic has general medical interest. Manuscripts will be accepted only if both their contents and style meet the standards required by the BIMJ.

Authorship information
Designate one corresponding author and provide a complete address, telephone and fax numbers, and e-mail address. The number of authors of each paper should not be more than twelve; a greater number requires justification. Authors may add a publishable footnote explaining order of authorship.

Group authorship
If authorship is attributed to a group (either solely or in addition to one or more individual authors), all members of the group must meet the full criteria and requirements for authorship described in the following paragraphs. One or more authors may take responsibility 'for' a group, in which case the other group members are not authors, but may be listed in an acknowledgement.

Authorship requirement
When the BIMJ accepts a paper for publication, authors will be asked to sign statements on (1) financial disclosure, (2) conflict of interest and (3) copyright transfer. The correspondence author may sign on behalf of co-authors.

Authorship criteria and responsibility
All authors must meet the following criteria: to have participated sufficiently in the work to take public responsibility for the content; to have made substantial contributions to the conception and design, and the analysis and interpretation of the data (where applicable); to have made substantial contributions to the writing or revision of the manuscript; and to have reviewed the final version of the submitted manuscript and approved it for publication. Authors will be asked to certify that their contribution represents valid work and that neither the manuscript nor one with substantially similar content under their authorship has been published or is being considered for publication elsewhere, except as described in an attachment. If requested, authors shall provide the data on which the manuscript is based for examination by the editors or their assignees.

Financial disclosure or conflict of interest
Any affiliation with or involvement in any organisation or entity with a direct financial interest in the subject matter or materials discussed in the manuscript should be disclosed in an attachment. Any financial or material support should be identified in the manuscript.

Copyright transfer
In consideration of the action of the BIMJ in reviewing and editing a submission, the author/s will transfer, assign, or otherwise convey all copyright ownership to the Clinical Research Unit, RIPAS Hospital, Ministry of Health in the event that such work is published by the BIMJ.

Acknowledgements
Only persons who have made substantial contributions but who do not fulfill the authorship criteria should be acknowledged.

Accepted manuscripts
Authors will be informed of acceptances and accepted manuscripts will be sent for copyediting. During copyediting, there may be some changes made to accommodate the style of journal format. Attempts will be made to ensure that the overall meaning of the texts are not altered. Authors will be informed by email of the estimated time of publication. Authors may be requested to provide raw data, especially those presented in graph such as bar charts or figures so that presentations can be constructed following the format and style of the journal. Proofs will be sent to authors to check for any mistakes made during copyediting. Authors are usually given 72 hours to return the proof. No response will be taken as no further corrections required. Corrections should be kept to a minimum. Otherwise, it may cause delay in publication.

Offprint
Contributors will not be given any offprint of their published articles. Contributors can obtain an electronic reprint from the journal website.

A RANDOMISED CONTROLLED TRIAL COMPARING INTRATHECAL FENTANYL-MORPHINE-BUPIVACAINE VERSUS INTRATHECAL FENTANYL-BUPIVACAINE IN WOMEN UNDERGOING CESAREAN SECTION.

Sudhirchandra SHAH [1], Dhadappa Damodar SRIDHARAN[1], Iqbal HUSSAIN[1], Thomas Abraham JACOBS[1], Maebelle CAYOWET[1], Chee Fui CHONG[2].

[1]Department of Anaesthesia, Suri Seri Begawan Hospital, Kuala Belait, Brunei Darussalam.
[2]Clinical Research Unit, Raja Isteri Pengiran Anak Saleha Hospital, Bandar Seri Begawan, Brunei Darussalam.

ABSTRACT

Objective: Comparison of the effectiveness and duration of Intrathecal fentanyl-morphine-bupivacaine versus intrathecal fentanyl-bupivacaine for post-operative analgesia after cesarean section. **Material and Method:** A prospective single blinded randomized controlled trial comparing intrathecal fentanyl-morphine-bupivacaine versus intrathecal fentanyl-bupivacaine for post-operative pain relief in caesarean section was conducted. Fifty parturient women, ASA physical status 1 and 2, were randomized into two groups. Group A received fentanyl 15 µgm, morphine 100 µgm and bupivacaine 10 mg intrathecally and Group B received fentanyl 25 µgm and bupivacaine 10 mg intrathecally. The primary outcome was quality and duration of postoperative analgesia. Block characteristic, haemodynamic variables, demand for rescue analgesia and adverse effects were also assessed. Intention to treat analysis was performed at the end of the study. P<0.05 was considered as statistical significance. **Results:** The demographic profiles and block characteristics were comparable in both groups except women in Group A underwent more additional procedures besides caesarean section (*p=0.044)*. The mean total morphine requirement post-operatively for the first 24 hours in Group A was 8.73 +/- 7.39 mg and Group B was 14.95 +/- 5.86 mg respectively, which was statistically significant *(p=0.004)*. Mean VAS score was also significantly lower in Group A *9p=0.049)* as was the need for additional analgesia *(p=0.024).* There were two cases of pruritus in Group B and one case of vomiting in Group A. There were no cases of respiratory depression. Fetal APGAR scores were similar in both groups. **Conclusion:** The use of intrathecal fentanyl-morphine-bupivacaine combination resulted in a more effective and longer duration of post-operative analgesia as compare to intrathecal fentanyl -bupivacaine in parturient women undergoing cesarean section under spinal anaesthesia.

Key words: Analgesia, Bupivacaine, Cesarean section, Fentanyl, Morphine, Post-operative, Spinal anaesthesia.

INTRODUCTION

Post-operative pain is an acute inflammatory response that is initiated by tissue trauma at the start of surgery and ends with healing of the tissue. Management of post-operative pain

Corresponding author: Dr Shah Sudhirchandra Dhansukhlal, Department of Anaesthesia, Suri Seri Begawan Hospital, Kuala Belait, Negara Brunei Darussalam. Hp: +6738674630; email: sudhirshah605@msn.com

begins even before surgery starts, especially so when surgery is being conducted under regional anaesthesia such as spinal anaesthesia. Ensuring a pain free procedure and post-operative period is a tricky balance between giving sufficient opioid to abolish the sensation of pain but also to avoid side effects of opioid overdose such as nausea and vomiting, dizziness, hypotension, pruritus and respiratory depression.[1]

Cesarean section operations, both elective and emergency, are usually carried out under spinal anaesthesia given via intrathecal route, in majority of patients worldwide. Opioids such as fentanly or morphine are commonly used in combination with bupivacaine for spinalanaesthesia. Numerous comparative studies, randomized controlled trials (RCTs) and meta-analyses have been carried out evaluating the different doses of intrathecal morphine or fentanyl with bupivacaine for spinalanaesthesia in CS.[2-15] Results have been consistent in that intrathecal fentanyl with bupivacaine, the former being lipophilic, get absorbed rapidly from the cerebrospinal fluid (CSF) into lipid tissue and into circulation after intrathecal injection. Thus, it has a rapid onset of action but produces only a short duration of analgesic effect lasting only up to 4 to 5 hours.[16] In comparison, intrathecal morphine with bupivacaine has longer duration of action, with post-operative analgesia that can last up to 12-27 hours because of its hydrophilic properties.[16,17] This hydrophilic properties enables morphine to binds to high affinity receptors in dorsal horn receptor sites, resulting in a smaller volume of distribution within the spinal cord but a sustained higher concentration in the CSF.[4] However, unlike fentanyl, morphine is slower in its onset of action (30-60 minutes), leading to inadequate intraoperative analgesia and also significantly higher rates of side effects such as post-operative pruritus, nausea and vomiting.[18]

Considering that fentanyl has rapid onset of action and morphine has longer duration of action, a combination of fentanyl and morphine in bupivacaine spinal anaesthesia may be ideal in maximizing the rapid onset and longer duration of analgesic effect. There are several RCTs to date that have compared intrathecal combination of fentanyl and morphine with either intrathecal morphine or fentanyl or diamorphine alone.[4,7-9,14,18] Results have been rather inconsistent, with some reporting positive findings while others reported no differences. These inconsistency may be related to the variation in doses of the opioids used in each of the studies.

All hospitals in Brunei Darussalam use a standard protocol of 25 µg of fentanyl added to 10 to 12 mg bupivacaine for spinalanaesthesia in CS, which provides very good intraoperative analgesia but most patients required some form of post-operative analgesia cover which is usually morphine. This study aims to evaluate whether using to combination of fentanyl and morphine with bupivacine compare to the current standard protocol of fentanyl with bupivacaine can improve the duration and quality of post-operative analgesic effect in parturient women undergoing cesarean section in Brunei Darussalam.

MATERIALS AND METHODS

Trial Design

This is a single blinded prospective randomized controlled study to compare the effectiveness of fentanyl-morphine combination versus fentanyl alone in bupivacaine during spinal anaesthesia in cesarean section for duration and quality of post-operative pain relief. This study was conducted at the Department of Anaesthesia with cooperation from the Obstetric Department, Suri Seri Begawan Hospital (SSBH), Kuala Belait, Brunei Darussalam from December 2018 to No-

vember 2019 over a period of 1 year.

Patient Population and Eligibility Criteria

All parturient women admitted to the Obstetric Department SSBH for elective or semi-emergency cesarean section were eligible for recruitment to the study if the inclusion and exclusion criteria were satisfied. Inclusion criteria were participants with ASA physical status of I or II with written informed consent for the study. Participants with significant co-morbid diseases such as significant cardiac, pulmonary or neurological disease, undergoing emergency cesarean section due to maternal or fetal compromise with life, ASA III and above, BMI >35 and those with known allergy to bupivacaine, fentanyl or morphine were excluded.

Allocation Concealment

A block randomization sequence of 4 and 6 was used to allocate participants to either fentanyl-morphine-bupivacaine or fentanyl-bupivacaine spinal anaesthesia. Randomization codes were generated using internet based randomization software.[19] The block randomization sequence was contained in a Microsoft Access database specifically designed for the trial. Participants recruited were randomly allocated using the onsite Microsoft Access database program with secured Login, using username and password. Patients and care-taker including post-operative ward staffs were blinded (Single Blinding) to the allocation.

Study Protocol

Fifty parturient women undergoing elective or semi-elective cesarean section who satisfied the above eligibility criteria were recruited to the study. Figure 1 shows the study protocol consort flow chart. All participants received explanation regarding the purpose of study, randomization process, blinding, the spinal procedure, post-operative pain control with patient controlled analgesia (PCA) and side effects of opioids. Written informed consents were obtained for participating in the study. A study information leaflet was also left with the participants for further information regarding the study.

Participants were randomized into Group A and Group B with 25 participants in each group. Group A participants received bupivacaine 10 mg, fentanyl 15 µg and morphine 100 µg while the control arm, Group B participants received the standard fentanyl 25 µg and bupivacaine 10mg given intrathecally for spinal anaesthesia in sitting position. Total volume injected for spinal anaesthesia was 2.5ml in each group. All participants received intravenous (iv) 10 mg metoclopramide and iv 50 mg ranitidine as premedication and iv Ondansetron 4 mg at the end of cesarean section to prevent nausea and vomiting. Post-operatively, all participants were started on PCA morphine with same protocol and monitored in the ward for 24 hours.

Data Collection and Management

Patients' demographics such as age, gravida status, parity, gestation age, past medical history and comorbidities, reasons for caesarean section and any additional operative procedures were recorded. Primary outcome measures such as VAS pain scores at 1, 6 and 24 hours, total morphine consumption in 24 hours via PCA and requirement for any additional analgesia as well as secondary outcomes such as APGAR score, sedation score and any opioid related side effects in the post-operative period were recorded. Participants' heart rate, blood pressure, respiratory rate and oxygen saturation post-operatively were also recorded into the specially designed proforma forms. All data collected were entered into an Access database/Excel and analyzed at the conclusion of the study.

Statistical Analysis

Based on preliminary results, with a study power of 80% at 5% significance, the sample size needed to show superiority of fentanyl-morphine-bupivacaine spinal anaesthesia over fentanyl-bupivacaine spinal anaesthesia

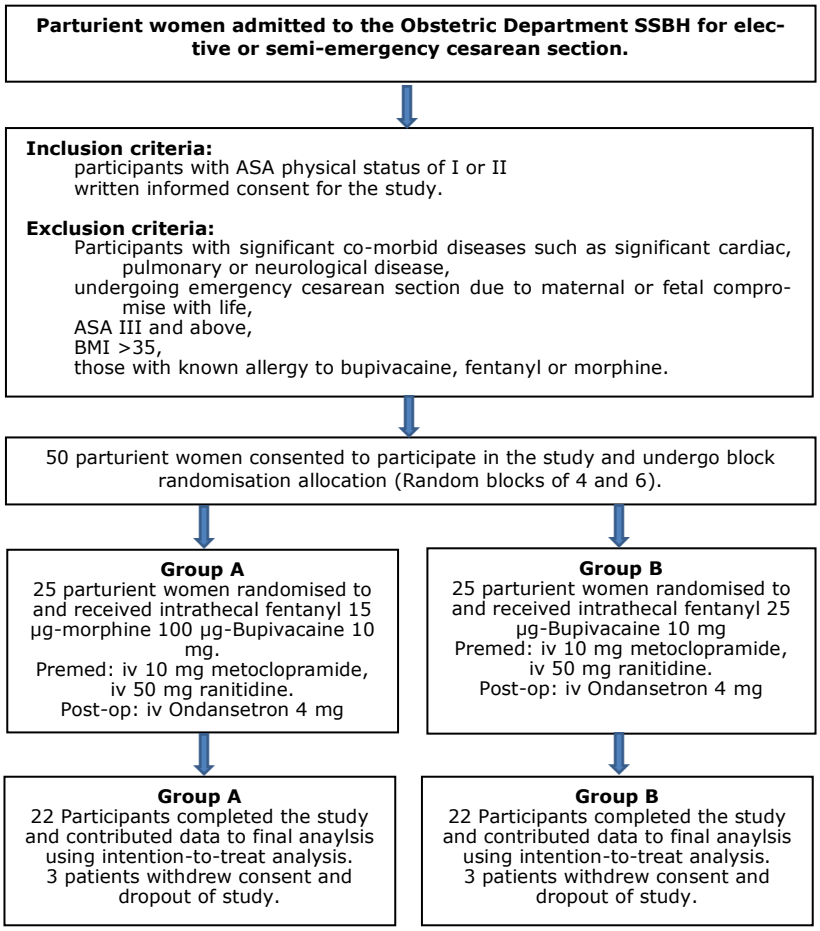

Figure 1: Study protocol consort flow chart.

morphine-bupivacaine spinal anaesthesia over fentanyl-bupivacaine spinal anaesthesia was 20 patients in each group. Assuming a dropout rate of 25%, a total of 50 patients were required, based on a 1:1 recruitment with 25 patients in each arm.

On completion of the study, the main analysis was carried out based on intention-to-treat principle. All statistical analysis was performed using SPSS statistics 20, IBM, USA. Statistical analysis for categorical data was carried out using Chi Square exact test. Differences between groups with normally distributed variables was tested using independent sample t-test. Variables with no normal distribution was tested using Mann-Whitney test. A $p < 0.05$ was considered statistically significant.

Study Ethics Consideration

This study was conducted in accordance with the principles of Good Clinical Practice Guidelines according to the Declaration of Helsinki, and all participants were not exposed to undue risk, and the data generated from the research were valid and accurate.[20] Participants' confidentiality were maintained throughout the study by using their randomised allocation code as their unique identifier, linked to their Bru-HIMs number only, which is a secure intranet database accessible via allocated staff's username and password. Participants who withdrew their consent from the study for whatever reasons were treated as dropouts and their data were removed from the final analysis. Ethics approval for the study was approved by Medical and Health Research and Ethics Committee based in RIPAS Hospital (MHREC/MOH/2018/1(1)).

RESULTS

A total of 50 patients were recruited to the study but six patients (3 from each group) withdrew from the study before completion and were excluded from the final analysis. Therefore, only 44 patients (22 in each group) were included in the final analysis (Figure 1).

Table I shows the patients' demographics and clinical characteristics of the two groups. Mean age of the participants in each group were about 32 years (Group A: 32.31 ± 5.34; Group B: 32.94 ± 6.59). There were not statistical differences between the two groups except for additional surgical procedures carried out. Group A has more additional procedures performed besides the caesarean sections than group B ($p<0.044$). Intra-operatively, none of patients in both groups complained of any pain and no additional opioid were required.

Table II shows the patients' post-operative data, morphine and additional analgesia requirements and VAS score between the two groups. Group A required significantly less morphine over 24 hours ($p=0.04$) and has lower VAS score ($p=0.049$) compared to Group B. Furthermore, fewer patients in Group A required additional analgesia than Group B which was also statistically significant (36.36% vs 59.09% respectively, $p=0.024$). This further support the spinal anaesthesia used in Group A is more effective in terms of reducing post-operative pain. All post-operative clinical parameters were not significantly different although in Group A, patients trended to have slightly lower blood pressure than Group B although this was not statistically significant. Mean SPO2 was just marginally higher in Group A than Group B but again there were no statistical differences. Despite using morphine for spinal induction, sedation score and fetal APGAR score were higher than measured in Group B but again there were no statistical significance observed. There were only two cases of pruritus reported post-operatively in Group B with one case of vomiting. There were no cases of nausea nor any patients developing respiratory distress in the post-operative period.

DISCUSSION

The results of our study clearly confirmed that the use of combination of fentanyl with morphine for spinal anaesthesia is superior to the standard protocol of fentanyl alone that is currently used in all hospitals in Brunei Darussalam for women undergoing CS. Both the mean total morphine requirement and mean VAS score in the first 24 hours post-operatively were significantly lower in the group (Group A) receiving intrathecal combination of fentanyl with morphine compared to group receiving standard protocol of fentanyl alone (Group B). The significantly lower mean VAS score in Group A was further reflected by a significantly lower requirement of additional analgesia in the first 24 hours post-operatively, compared to Group B. On the contrary, Group A had significantly more additional procedures such as tubal ligation and forceps or vacuum suction performed during the CS, compared to Group B. These additional procedures would have incurred longer duration of operation and even more pain post-operatively but this is not reflected in total mean VAS score or mean total morphine requirement or the need for additional analgesia in Group A.

There are only two other RCTs to date that compared intrathecal fentanyl in combination with morphine with fentanyl alone.[4,7] Most other RCTs compared intrathecal fentanyl and morphine combination to morphine alone.[8,9,14] The first study was by Sibilla et al in 1997, who compared intrathecal morphine (100 µg) and fentanyl (25 µg) alone or in combination (fentanyl 25 µg plus morphine 100 µg).[4] He reported that both intrathecal morphine alone and in combination were sig-

Table I: Participants' pre-operative demographic and clinical variables. Group A: Fentanyl 15µg-Morphine 100µg -Bupivacaine 10mg; Group B: Fentanyl 25µg-Bupivacaine 10mg.

Variables	Group A	Group B	*p*
Total number	22	22	
Mean Age (+SD) in years	32.31 ± 5.34	32.94 ± 6.59	*0.727*
Gravida Status	3.14 ± 1.46	2.73 ± 1.32	*0.334*
Para Status	2.00 ± 1.45	2.18 ± 2.08	*0.637*
Gestational Status (Weeks)	37.75 ± 0.76	37.92 ± 1.78	*0.686*
Co-morbidities			
None	7	9	
Congenital VSD	1	0	
Heart Valve disorders	1	0	
Gestation Hypertension/Hypertension/Pre-eclampsia	2	4	
Diabetes Mellitus/Gestational DM	3	7	
Thalassemia	2	2	
Intrauterine growth retardation	1	0	
Tubal cyst	1	0	*0.933*
myomectomy for huge fibroid	1	0	
HOCM,WPW	1	0	
Anaemia	1	1	
Deafness	1	0	
Asthma	0	2	
Hepatitis C	0	1	
Hypothyroidism	0	2	
Past Pregnancy history			
None	9	8	
Previous LCSC	13	11	
Twin pregnancy	0	1	*0.975*[¥]
Breech	2	2	
Pregnancy induced hypertension	0	1	
Post-partum haemorrhage	2	0	
Reasons for Cesarean Section			
Elective/Patient's request	8	4	
Previous LCSC	6	6	
Breech presentation/Unstable Lie	6	3	
Fetal distress	1	0	*0.906*[¥]
Placenta previa	1	0	
Twin pregnancy	0	1	
Failure to Progress	0	8	
Additional surgical procedures			
None	10	14	
Bilateral tubal ligation	11	8	***0.044****[¥]
Vacuum suction/Forceps	2	1	

* Statistical significance, *p<0.05*

For continuous data, two sample t-test was used for statistical analysis

[¥]For categorical data, Fisher exact test was used for statistical analysis

Table II: Postoperative Data, morphine requirements and VAS score between the two groups. Group A: Fentanyl 15µg-Morphine 100µg-Bupivacaine 10mg; Group B: Fentanyl 25µg-Bupivacaine 10mg.

Variables	Group A	Group B	*p*
Mean total morphine requirements (mg)	**8.73 ± 7.39**	**14.95 ± 5.86**	***0.004****
Mean VAS Score	**2.35 ± 2.03**	**3.44 ± 1.49**	***0.049****
Mean Systolic BP	113.50 ± 12.58	122.89 ± 18.46	*0.056*
Mean Diastolic BP	71.92 ± 7.65	75.52 ± 9.67	*0.179*
Mean Heart Rate	80.29 ± 8.84	78.01 ± 11.50	*0.464*
Mean Respiratory rate	19.69 ± 1.03	19.83 ± 1.22	*0.698*
Mean SPO2	98.53 ± 0.72	98.11 ± 0.80	*0.071*
Mean Sedation Score	0.10 ± 0.28	0.19 ± 0.51	*0.473*
Mean Foetal APGAR Score	9.23 ± 1.07	9.18 ± 0.66	*0.866*
Use of additional analgesia[#], n(%)	8(36.36%)	13(59.09%)	***0.024****
Complications			
Pruritis	0	2	
Nausea and Vomiting	1	0	
Respiratory distress	0	0	

* Statistical significance, *p<0.05*

[¥#] (Rescue Analgesia used - Pethidine, Paracetamol, Diclofenac or combo, in suppository or IV form.)

nificantly better in terms of duration and quality of post-operative analgesia as well as significantly lower mean post-operative pain score than fentanyl alone. Patients who received intrathecal fentanyl alone anaesthesia reported mean duration of effective analgesia of 4.61 hours ranging from 0.51 hours to 8 hours post-operatively while patients receiving either morphine or in combination with fentanyl had mean effective analgesia duration of 14-20 hours, ranging from 9.7 hours to over 24 hours. This findings is similar to our own findings, although we only compared intrathecal morphine in combination with fentanyl to fentanyl alone. Sibilla et al further reported that a significantly lower proportion (30%) of women who received combination intrathecal fentanyl and morphine anaglesia required additional post-operative analgesia during the first 12 hours after cesarean section, compared to 70% of women receiving fentanyl alone spinal anaglesia, in the same time interval.[4]

second more recent RCT by Karaman et al in 2011, compared intrathecal morphine (200 µg) and fentanyl (25 µg) alone or in combination (fentanyl 12.5 µg plus morphine 100 µg) but reported that intrathecal morphine alone was significantly better than fentanyl alone or in combination in terms of effective post-operative analgesia.[7] However for this study, the intrathecal morphine alone dose used was double that in the Sibilla et al and our studies while the combination fentanyl dose was half.[4] This difference in doses of the study drugs may have accounted for the difference in results. Despite halving the fentanyl dose in the intrathecal combination group, the reported mean effective duration of post-operative analgesia was 12.7 hours which was just slightly less than the 13.99 hours reported by Sibilla et al. Similarly in our study, with a slightly higher dose of fentanyl at 15 µg in the combination group, than the Karaman's study, we were able to show significantly better effectiveness and duration of post-operative analgesia in the intrathecal fentanyl-morphine-bupivacaine group.

Intraoperative pain has been report in 18% to 29% of cases after administration of intrathecal morphine alone at a dose of 0.1 to 0.2 mg.[13-15,21,22] In our study, none of the patients complained of any intra-operative pain nor did they require any additional opi-

oids in the intra-operative period. For our study, we elected to use fentanyl 15 µg in combination with morphine 100 µg, in addition to bupivacaine for our spinal anaesthesia. Sibilla et al and Karaman et al both reported in their studies that there were no significant differences in terms of quality of intra-operative analgesia between the 3 groups. Furthermore, several studies have previously reported that increasing doses of opiods either fentanyl (>50 µg) or morphine (>100 µg) does not significantly improve the effectiveness of intra-operative analgesia nor extend the duration of post-operative analgesia.[11,12,27,29,30]

Post-operative complications associated with intrathecal opioid used has been well documented in several RCTs.[4-12] Minor complications such as pruritus, nausea, vomiting and even urinary retention are generally troublesome rather than life threatening and are due to µ and K opioid receptor activations.[21] In our study, two participants in Group B had pruritus and one in Group A had vomiting in the post-operative period. There were no cases of nausea. Dahl et al in their systematic review of intrathecal opiods for cesarean section predicted that for every 100 women who are given intrathecal morphine at 100 µg dose, 43% will experience pruritus and 10-12% will complain of nausea and vomiting, which is in excess of what is observed in our study.[13]

A major concern with regards to intrathecal morphine anaesthesia is the risk of respiratory depression. In our study, no participant had respiratory rate less than 8 and SPO2 was maintained well above 95% in all participants post-operatively. In fact, the incidence of respiratory distress with the use of intrathecal morphine is generally low and has been reported in a prospective study of 856 women undergoing intrathecal morphine anaesthesia, only 8 patients reportedly developed respiratory distress in the post-operative period, accounting for less than 1% and this was associated with a higher dose of intrathecal morphine of 200 µg.[31] In another study, the author reported one case of respiratory depression 14 hours after administration of 0.1 mg intrathecal morphine in addition to bupivacaine which was attributed to post-operative parenteral opioid consumption (24 mg morphine) by PCA rather than spinal opioid.[6]

Sedation score in our study is generally low in both groups, although surprisingly, it was twice as low in the combination Group A than fentanyl alone Group B, but there was no statistical difference. Opioids administered via the central route such as in spinal anaesthesia is generally associated with much lesser sedation than the parenteral route or in doses exceeding commonly used in current clinical practice .[7,31]

There was no relationship between intrathecal opioid administration and neonatal Apgar scores in our study (Table II), and this finding is in agreement with other reports.[4,24-27] In fact the fetal APGAR score were noted to be slightly higher in Group A than in Group B but this was not statistical significant.

CONCLUSION

The addition of intrathecal morphine added to fentanyl and bupivacaine in our study resulted in a more effective and longer duration of post-operative analgesia as compare to intrathecal fentanyl and bupivacaine in parturient women undergoing cesarean section under spinal anaesthesia. Health authorities in all Hospitals in Brunei Darussalam should consider changing their current standard protocol of intrathecal fentanyhl-bupivacine regime to intrathecal combination fentanyl-morphine-bupivacaine regime which will be more effective and beneficial to our parturient clients attending our delivery services. Future study to evaluate the financial cost effective-

ness of this regime can be undertaken to provide further support for the use of this intrathecal combination regime for spinal anaesthesia in cesarean section.

CONFLICT OF INTEREST

None

ACKNOWLEDGEMENT

Advisory support: Ministry of Health, Brunei Darussalam, Dr Hj Zulaidi bin Hj Latif, Deputy Permanent Secretary, MOH.

REFERENCES

1: Chou R, Gordon DB, de Leon-Casasola OA, Warner L, Weisman SJ, Wu CL. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia. The Journal of Pain. 2016;17(2):131-157. [Accessed on 10 December 2020].

2: G Siti Salmah, MD, Y C Choy. Comparison of Morphine with Fentanyl Added to Intrathecal 0.5% Hyperbaric Bupivacaine for Analgesia After Caesarean Section. Med J Malaysia. 2009;64(1):71-4. [Accessed on 10 December 2020].

3: Gerancher JC, Herbert F, Eisenach J. Determination of an effective dose of intrathecal morphine for pain relief after Caesarean section delivery. Anesthesia and Analgesia 1999;88 (2):346-51. [Accessed on 10 December 2020].

4: Sibilla C, Albertazz P, Zatelli R, et al. Perioperative analgesia for Caesarean section: comparison of intrathecal morphine and fentanyl alone or in combination. International Journal Obstetric Anaesthesia. 1997;6:43-8.

5: Palmer CM, Emerson S, Volgoropoulus D, Alves DRN. Dose response relationship of intrathecal morphine for post-Caesarean analgesia. Anesthesiology 1999;90(2):437-44. [Accessed on 10 December 2020].

6: Swart M, Sewell J, Thomas D. Intrathecal morphine for Caesarean section: an assessment of pain relief, satisfaction and side effects. Anaesthesia 1997;52: 373-7. [Accessed on 10 December 2020].

7: Karaman S, Günüsen I, Uyar M, Biricik E, Fırat V. The effects of morphine and fentanyl alone or in combination added to intrathecal bupivacaine in spinal anesthesia for cesarean section. Agri. 2011;23(2):57-63. [Accessed on 10 December 2020].

8: Thornton P, Hanumanthaiah D, O'Leary RA, Iohom G. Effects of fentanyl added to a mixture of intrathecal bupivacaine and morphine for spinal anaesthesia in elective caesearean section. Rom J Anaesth Intensive Care. 2015;22(2):97-102. [Accessed on 10 December 2020].

9: Weigl W, Bieryło A, Wielgus M, Krzemień-Wiczyńska Ś, Kołacz M, Dąbrowski MJ. Perioperative analgesia after intrathecal fentanyl and morphine or morphine alone for cesarean section: A randomized controlled study. Medicine (Baltimore). 2017;96(48):e8892. doi: 10.1097/MD.0000000000008892. [Accessed on 10 December 2020].

10: Caranza R, Jeyapalan I, Buggy DJ. Central neuraxial opioid analgesia after caesarean section: comparison of epidural diamorphine and intrathecal morphine. Int J Obstet Anesth 1999;8:90–3.

11: Abboud TK, Dror A, Mosaad P, et al. Mini-dose intrathecal morphine for the relief of post-cesarean section pain: safety, efficacy, and ventilatory responses to carbon dioxide. Anesth Analg 1988;67:137–43. [Accessed on 10 December 2020].

12: Milner AR, Bogod DG, Harwood RJ. Intrathecal administration of morphine for elective caesarean section. A comparison between 0.1 mg and 0.2 mg. Anaesthesia 1996;51:871–3. [Accessed on 10 December 2020].

13: Dahl JB, Jeppesen IS, Jorgensen H, et al. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: a qualitative and quantitative systematic review of randomized controlled trials. Anesthesiology 1999;91:1919–27. [Accessed on 10 December 2020].

14: Connelly NR, Dunn SM, Ingold V, et al. The use of fentanyl added to morphine-lidocaine-epinephrine spinal solution in patients undergoing cesarean section. Anesth Analg 1994;78:918–20. [Accessed on 10 December 2020].

15: Girgin NK, Gurbet A, Turker G, et

al. Intrathecal morphine in anesthesia for cesarean delivery: dose-response relationship for combinations of low-dose intrathecal morphine and spinal bupivacaine. J Clin Anesth 2008;20:180–5.

16: Wolfgang C. Ummenhofer, Rosalin H. Arends, Danny D. Shen, Christopher M. Bernards. Comparative Spinal Distribution and Clearance Kinetics of Intrathecally Administered Morphine, Fentanyl, Alfentanil, and Sufentanil. Anesthesiology 2000;92:739–53. [Accessed on 10 December 2020].

17: Kalindi A DeSousa, Rajkumar Chandran, Intrathecal morphine for postoperative analgesia: Current trends. World J Anesthesiol 2014;3(3):191-202. [Accessed on 10 December 2020].

18: Barkshire K, Russell R, Burry J, et al. A comparison of bupivacaine-fentanyl-morphine with bupivacaine-fentanyl-diamorphine for caesarean section under spinal anaesthesia. Int J Obstet Anesth 2001;10:4–10.

19: Sealed Envelope. Create a block randomisation list. 2018. [Accessed on 27 August 2018]. Available at https://www.sealedenvelope.com/simple-randomiser/v1/lists

20: World Health Organization. Handbook for good clinical research practice (GCP) guidance for implementation. Geneva, Switzerland: World Health Organization; 2005. [Asssessed on 27 August 2018].

21: Chung CJ, Yun SH, Hwang GB, et al. Intrathecal fentanyl added to hyperbaric ropivacaine for cesarean delivery. Reg Anesth Pain Med 2002;27:600–3.

22: Sultan P, Halpern SH, Pushpanathan E, et al. The effect of intrathecal morphine dose on outcomes after elective cesarean delivery: a meta-analysis. Anesth Analg 2016;123:154–64. [Accessed on 10 December 2020].

23: Baraka A, Noueihid R, Hajj S. Intrathecal injection of morphine for obstetric analgesia. Anesthesiology 1981;54:136–40. [Accessed on 10 December 2020].

24: Stoelting RK. Pharmacology & physiology in anesthetic practice, 3th ed. Philadelphia: Lippincott Company. Williams & Wilkins. 1999:77-181.

25: Culebras X, Gaggero G, Zatloukal J, et al. Advantages of intrathecal nalbuphine, compared with intrathecal morphine, after cesarean delivery: an evaluation of postoperative analgesia and adverse effects. Anesth Analalg 2000;91:601–5. [Accessed on 10 December 2020].

26: Braga AA, Frias JA, Braga FS, et al. Spinal anesthesia for cesarean section. Use of hyperbaric bupivacaine (10 mg) combined with different adjuvants. Rev Bras Anestesiol 2012;62:775–87. [Accessed on 10 December 2020].

27: Hunt CO, Naulty JS, Bader AM, et al. Perioperative analgesia with subarachnoid fentanyl-bupivacaine for cesarean delivery. Anesthesiology 1989;71:535–40. [Accessed on 10 December 2020].

28: Shende D, Cooper GM, Bowden MI. The influence of intrathecal fentanyl on the characteristics of subarachnoid block for caesarean section. Anaesthesia 1998;53:706–10. [Accessed on 10 December 2020].

29: Chu CC, Shu SS, Lin SM, Chu NW, Leu YK, Tsai SK, et al. The effect of intrathecal bupivacaine with combined fentanyl in cesarean section. Acta Anaesthesiol Sin 1995;33(3):149-54.

30: Belzarena SD. Clinical effects of intrathecally administered fentanyl in patients undergoing cesarean section. Anesth Analg 1992;74 (5):653-7. [Accessed on 10 December 2020].

31: Abouleish E, Rawal N, Rashad MN. The addition of 0.2 mg subarachnoid morphine to hyperbaric bupivacaine for cesarean delivery: a prospective study of 856 cases. Reg Anesth 1991;16(3):137-40.