Analgesic effect of intrathecal morphine combined with low dose bupivacaine on postoperative analgesia after liver resection: A randomized, controlled preliminary study

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Directed by Professor Bon-Nyeo Koo

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ABSTRACT

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Purpose: Efficient postoperative pain control plays a vital part in management of patients after major surgeries including hepatectomy. A current method of postoperative pain control envelopes a multimodal approach including intrathecal injection including morphine and a local anesthetic. However, high doses of bupivacaine may inadvertently cause unwanted side effects. The purpose of this study is to compare the effects of intrathecal morphine injection and low dose bupivacaine with morphine injection.

Methods: Patients receiving hepatectomy were included and divided into three groups. Each patient received an intrathecal injection immediately prior to induction of general anesthesia based on their group allocation: (1) sham injection for the control group; (2) morphine 400mg for the morphine group (M); (3) morphine 400mcg and bupivacaine 5mg for the morphine and bupivacaine group (M+B). Our primary outcome was time to first rescue analgesic. VAS (visual analogue scale) pain score was compared until POD (postoperative day) 1. Total fentanyl dose administered by patient controlled analgesia was recorded until POD2. Side effects were monitored until POD 3 for any residual effects.

Results: Although time to first rescue was significantly shorter in the control group compared to group M and group M+B ($p<0.001$). both groups were comparable to each other. Although there was a significant decrease in VAS score and total fentanyl administration via PCA (patient-controlled analgesia) in group M and group M+B compared to the control group, there was no difference between the intervention groups. The control group required more rescue analgesic compared to group M and group M+B; however, there was no difference between the intervention groups. Pruritus was more prevalent in M+B group compared to the control group ($p=0.023$) and tingling was significantly higher in the M+B group compared to the other groups ($p=0.010$).

Conclusion: Addition of 5mg bupivacaine may be insufficient in providing further analgesic benefits; however higher doses may aggravate side effects. Further studies are warranted to investigate optimal regimen for intrathecal postoperative pain control against complications.

Key words: intrathecal, bupivacaine, analgesia

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I. INTRODUCTION

Effective postoperative pain control plays a vital part in management of patients after major surgeries including hepatectomy. A proper postoperative pain control plan will promote patient satisfaction while decreasing time to ambulation, respiratory and cardiovascular complications, and consequently mortality.(1, 2) Recently, a multimodal approach rather than a pain control method relying on opioids alone has been advocated to control postoperative pain more effectively while reducing the side effects of drugs.(3) The Enhanced Recovery After Surgery (ERAS) guidelines emphasizes the significance of multimodal analgesia, and the goal to optimizing postoperative analgesia while avoiding potential side effects is increasingly becoming a primary interest after major operations including liver resection.(4)

One method to the multimodal approach includes a postoperative epidural patient-controlled analgesia (PCA). However, for liver resection patients due to the possible complications from coagulopathies, cost-effectiveness of the procedure, and excessive sympathetic block by epidural analgesia, continuous placement of an

epidural catheter has been debated against.(5-8) Intrathecal morphine with the combined use of an IV PCA is a method that avoids the potential complications of an epidural catheter and studies have shown that the analgesic effects are not reduced compared to an epidural.(8-10) Guidelines for liver surgery published by ERAS strongly recommended intrathecal opioids instead of epidural analgesia as part of multi-modal analgesia.(11, 12)

Intrathecal morphine used as a 'one-shot' method provides several advantages as it is easy, cost-effective, reliable and technical failures are rare.(13) The analgesic effects last for 20-48 hours.(14, 15) However, because of the hydrophilic properties of morphine, the peak effect time of an intrathecal injection is 6 hours, which means morphine alone may not be adequate for immediate post-operative pain control.(10) To compensate for that time, there have been studies that suggest a combination using a local anesthetic such as bupivacaine is effective during this period. However, the possible complications and optimal dose have not been evaluated sufficiently against liver resection. Although there are previous studies that suggested a high dose of bupivacaine could induce undesired excessive motor block and hemodynamic changes during surgery, there is lacking evidence of the effects of lower dose of bupivacaine.(16) Koning et al suggested that addition of 12.5mg bupivacaine to morphine during robot assisted radical prostatectomy reduced opioid consumption and was a viable multimodal analgesic postoperative method.(14) A lower dose of 5mg combined with morphine was compared against saline to shown to be effective in lowering pain scores and opioid consumption without adverse effects. Although bupivacaine may induce unwanted side effects after surgery including motor block, sensory block, and tingling sensation, there are no studies that investigate whether low dose bupivacaine would have synergistic or additional analgesic effects to intrathecal morphine while reducing any risk of side effects, with respect to postoperative pain control.

The aim of our study was to compare the effectiveness and side effects of intrathecal

morphine combined with low dose bupivacaine against intrathecal morphine alone and no intrathecal injection. We hypothesized that the addition of a low dose bupivacaine would provide improved immediate postoperative analgesia and delay the time to first rescue analgesics. Also, we compared opioid consumption and pain scores during the initial 48 hours, and side effects in the first 72 hours postoperative.

II. MATERIAL AND METHODS

After Institutional Review Board (IRB no. 4-2018-0838) approval, we conducted a single center, double blinded randomized prospective clinical trial in a teaching hospital from October 2018 to April 2020. Patients over the age of 19 years old scheduled for liver resection under open or laparoscopic surgery are eligible for participation. Exclusion criteria included: contraindication to spinal anesthesia (including coagulation disorders, increased intracranial pressure, severe systemic infection); contraindication to study medication (including allergies); patients with psychological or neurological disorders that affect pain assessment; patients with severe respiratory, heart, or kidney disease; and patients unable to read the consent form (including illiteracy, mental disorders).

Patients were informed about the purpose and method of the study. After explanation, the patient was revisited at least 1 day after initial explanation and written consent was taken. Explanation of the purpose of the study and written consent was conducted in an independent counseling office in the ward

On the day of surgery, the study subjects were randomly divided into three groups using a random number table: (1) control group; (2) morphine administration group (Group M); (3) or morphine + bupivacaine administration group (Group M + B). Patient group assignment, drug preparation, and drug administration was provided by a trained anesthesiologist. The patient, surgical team, nurses on the ward, and researchers were blinded to allocation.

1. Intrathecal injection

Upon arrival to the operating room, standard monitoring including electrocardiogram, non-invasive blood pressure monitor, pulse saturation was placed after confirming the patient. All patients received an intrathecal injection prior to general anesthesia. Patients were placed in a lateral decubitus position and after performing skin sterilization, a trained anesthesiologist infiltrated the skin with 1% lidocaine using a 25G needle for local anesthesia.

In the control group, a sham procedure of 2 ml of 1% lidocaine injected percutaneously using the initial 25G needle used for local anesthesia was performed. For Group M and Group M + B, after confirming proper placement of the needle in the spinal canal by cerebrospinal fluid using a 25G pencil-point spinal needle, 400mcg of morphine or 400mcg of morphine with 5mg of 0.5% bupivacaine chloride was injected, respectively. The patient was positioned back into the supine position and after 5 minutes, we checked the spread of dermatome to spinal injection using an alcohol swab to test at which point the patient felt sensory loss.

2. Anesthesia method

For all groups, standardized general anesthesia typical to liver resection was administered after spinal puncture. Pre-medication with glycopyrrolate 0.1mg IV was administered before induction of anesthesia. Induction of anesthesia was performed with propofol and remifentanil and injection of 0.6mg/kg rocuronium for sufficient muscle relaxation and tracheal intubation. Anesthesia was maintained with total intravenous anesthesia; propofol sustained with an infusion of propofol-TCI using the target concentration control injector Marsh model, and remifentanil maintained in a remifentanil-TCI continuous infusion using the Minto model. For the hemodynamic monitoring during surgery, arterial cannulation and intravenous cannulation was performed.

During surgery, blood pressure, central venous pressure, and cardiac output were

continuously monitored. In cases of hypotension (blood pressure or heart rate within 20% of the baseline), blood pressure was controlled by adjusting the anesthetic concentration, fluid supply, blood transfusion or inotropes, or vasopressor depending on the cause. In addition, a bispectral index (BIS) monitor capable of checking the depth of anesthesia during surgery was applied and anesthesia depth was maintained between 40-60. FloTrac/Vigileo System was used to monitor cardiac index, stroke volume variation (SVV), systemic vascular resistance index (SVRI) and mean arterial pressure (MAP). We managed fluid therapy using goal directed strategy (SVV <13%, MAP > 75 mmHg, CI >= 2.0 L/min/m^2, SVRI <= 3000 dynes•sec/cm^5/m^2). All procedures are standardized in our institute.

After closure of the peritoneum, fentanyl 1•BW (mcg) and nefcom 40mg was administered intravenously for postoperative pain control, and 0.3mg ramosetron for prevention of nausea and vomiting.

At the end surgery, propofol and remifentanil infusions were ceased and neostigmine and glycopyrrolate were used to reverse muscle relaxation. When the patient's consciousness and muscle relaxation was restored, we extubated the patient and transferred the patient to the post- operative anesthesia care unit (PACU). All patients received intravenous patient-controlled analgesia (IV PCA) regimen, which was started at the end of surgery, as follows; Fentanyl 15 * BW (mcg) with ramosetron 0.6mg and normal saline to a total volume of 100 ml. Infusion rate was set at 1 ml per hour with a bolus of 1ml and a lockout time of 7minutes.

3. In the PACU

Standard vital signs monitoring including 3-lead ECG, blood pressure, and oxygen saturation were monitored in the PACU. At 30 and 60 minutes upon entering the PACU, an anesthesiologist blind to the patients' assignment assessed whether the patient presented any side effects of the intrathecal injection by assessing the patient's sensory and motor block levels and whether the patient has a tingling sensation.

Patient presenting with sensory and motor block levels were observed in the PACU until the sensory or motor block dissipated. Also, any possible adverse reactions to intrathecal injection including headache, nausea, vomiting, pruritus, shivering, respiratory depression, decreased consciousness, and hypotension, were recorded. At any time of this study, respiratory depression was defined as defined as less than or equal to 8 breaths/min. Hypotension was defined as a 15% decrease in systolic blood pressure from baseline.

The anesthesiologist also assessed the patient for pain using the visual analogue scale(VAS) in the PACU at 30 and 60 minutes to compare immediate postoperative pain control amongst the groups. If the patient presented with a pain score of VAS 5 or higher, Fentanyl 1 μg/kg IV was administered

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4. In the ward

In the ward, a researcher, blind to the patient's assignment group, checked the patient for possible side effects including sensory and motor block level, tingling sensation, headache, nausea, vomiting, pruritus, respiratory depression, decreased consciousness, and hypotension on the night of surgery and on the day after surgery. To compare postoperative pain control among the groups, pain score using VAS was assessed on the night of the surgery and day after surgery. For further assessment of pain control, the number of painkillers administered on postoperative day (POD) 1,2,3 and the total dose of fentanyl administered through IV PCA was recorded. Also, we checked the time to ambulation for each patient.

5. Rescue analgesics

If the patient complained of pain score of 5 or higher on the VAS scoring system, despite the use of IV-PCA in the ward, rescue analgesic (intravenous pethidine 25mg) was given. To compare the effectiveness of the analgesia, we compared whether the patients received a first rescue analgesic and if they did, the time to the first rescue

analgesic. Also, subsequent rescue analgesics administered on the POD 1,2,3 was recorded. Total analgesic consumption was recorded in the first 24 hours postoperation and on the following POD 2 and 3.

6. Power of study

The primary end point was the time to first rescue analgesic in the first 72 hours.
To detect a difference of one SD between the mean of the time to first rescue analgesic (1), a sample size of 28 patients for each group would be required to have a power of 80% with α=0.025 (one-sided hypothesis). Taking into consideration the potential for drop-outs, we decided to enroll 30 patients per group.
Data are expressed as mean ± SD of the mean for continuous values or median with interquartile range for discontinuous values. The time to first rescue was described as a median and interquartile range (IQR) and values were compared by the Kaplan-Meier statistic. Distributions were examined to ensure proper statistical treatment. Data were analyzed for normal distribution and One-way ANOVA with Bonferroni correction for multiple comparisons was performed for continuous data. For ordinal data, Chi-Square Test was used. A p value <0.05 was deemed statistically significant and a p value<0.01 was deemed statistically significant for secondary outcomes after correction. Values were calculated with Statistical Package for Social Scienced statistical software (SPSS 23.0, USA).

III. RESULTS

A total of 91 patients were screened for enrollment, of whom 1 patient was not included due to the cancellation of surgery. 4 patients withdrew consent after random allocation, during the period of the study. A total of 86 patients were analyzed with 28 patients in the control group, 28 patients from Group M, and 30 patients in Group M+B. Demographics and surgical characteristics were balanced at the baseline shown in Table 1.

Table 1. Demographic data and intraoperational characteristics

	Group Control (n=28)	Group M (n=28)	Group M+B (n=30)	p
Sex				0.629
Male	21(57.0%)	19(67.9%)	19(63.3%)	
Age	44.9±17.9	43.0±14.4	38.2±13.1	0.217
Body weight (kg)	71.1±10.8	66.6±10.2	66.8±11.2	0.224
Height (cm)	170.8±8.3	167.2±9.8	166.9±9.0	0.199
BMI (kg/m^2)	24.3±2.8	23.5±1.9	23.9±2.8	0.487
Anesthesia time (min)	346.1±135.5	410.4±102.5	411.8±103.4	0.053
Operation time (min)	280.3±131.5	336.4±100.9	338.3±99.4	0.089
Operation type				0.752
Open	16(57.1%)	17(60.7%)	20(66.7%)	
Laparoscopy	12(42.9%)	11(39.3%)	10(33.3%)	
Extent of resection				0.557
Right lobe	15(53.6%)	19(67.9%)	23(76.7%)	
Left lobe	4(14.3%)	4(14.3%)	2(6.7%)	
Central	1(3.6%)	1(3.6%)	0(0.0%)	
Segment	8(28.6%)	4(14.3%)	5(16.7%)	
Extubation time (min)	15.9±12.9	13.6±6.3	14.7±4.8	0.634

BMI: body mass index

Extubation time was defined from the moment anesthetics were ceased until the patient was extubated.

The numbers are mean ± SD or number of patients (percentage, %).

The median (IQR) time to first rescue, our primary endpoint, was 13(8-18) min for the control group, which was significantly shorter compared to group M and group M+B (60(34-86) min vs 70(21-118) min, p<0.001); however, there was no significant difference between group M and M+B as shown in Figure 1.

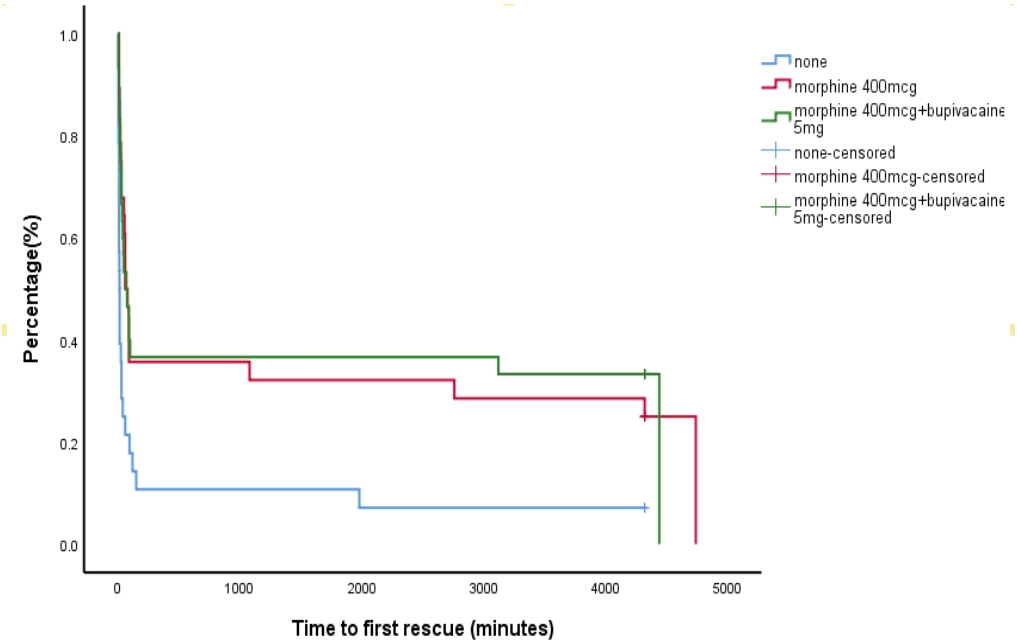

Fig. 1 Kaplan-Meier analysis of the time to first rescue analgesic The comparison of time to first rescue between the three groups show that the control group had a significantly shorter time compared to the intervention groups which show comparable graph curves.

There was a significant reduction in mean VAS score in group M+B and group M compared to the control group until POD 1, however, there was no significant difference in VAS scores at any time point between group M and group M+B (Table 2). Patients in the control group required more rescue analgesics compared to both the M group and the M+B group on POD 1 (p<0.001). There was no difference in rescue analgesics between group M and M+B group. (Table 2). On POD 2 and 3, there were no significant differences among groups. (p=0.0702, p=0.159 respectively)

Table 2. Pain Score and additional analgesics requirement in postoperative period

VAS: visual analogue scale, PACU: post-operative anesthesia care unit, POD: postoperative

	Group Control (n=28)	Group M (n=28)	Group M+B (n=30)	p
VAS in PACU (30 min)	6.1±2.6	3.7±1.9*	4.1±2.9*	0.001
VAS in PACU (60 min)	5.5±2.4	3.4±1.9*	3.3±2.4*	<0.001
VAS on operation night	4.4±1.7	2.6±1.3*	2.4±1.2*	<0.001
VAS POD1	3.5±1.5	2.4±1.7*	2.2±1.1*	0.002
IV PCA Fentanyl Dose(mcg) Op night	227.3±117.9	122.1±58.8*	136.6±63.3*	<0.001
IV PCA Fentanyl Dose(mcg) POD 1	365.7±218.0.	214.0±166.7*	253.6±142.9*	0.006
IV PCA Fentanyl Dose(mcg) POD 2	176.3±147.6	210.0±159.8	226.3±172.3	0.488
Additional analgesics POD 1	1.5±1.4	0.3±0.6*	0.3±0.6*	<0.001
Additional analgesics POD 2	0.5±0.8	0.5±0.7	0.3±0.8	0.702
Additional analgesics POD 3	0.3±0.5	0.5±1.1	0.2±0.4	0.159

operative day, IV: intravenous, PCA: patient-controlled analgesia
The numbers are mean ± SD or number of patients (percentage, %).
*p<0.001 vs. group Control

Patients in the control group required more rescue analgesics compared to both the M group and the M+B group on POD 1 (p<0.001). There was no difference in rescue analgesics between group M and M+B group. (Table 2). On POD 2 and 3, there were no significant differences among groups. (p=0.0702, p=0.159 respectively) (Table 2) Fentanyl dose administered by PCA was significantly lower in group M and group M+B compared to the control group on op night (p<0.001) until POD 1 (p=0.006),

with no difference on POD 2 (p=0.488). There was no difference between fentanyl dose between group M and group M+B throughout the study period until POD2 (Table2).

Twelve patients in the M+B group (40%) presented with sensory block compared to 0 patients in the control group ~~a~~nd 2 patients in the M group (7.1%) (p<0.001). Four patients in the M+B group (13.3%) showed motor block compared to 0 patients in control group and 1 patient in the M group (p=0.079). All cases of sensory and motor block were resolved before leaving the PACU. Side effects are shown in Table 3. All 6 patients that experienced tingling in the first 72 hours were from the M+B group (p=0.010). Out of the 14 patients that experienced pruritus, 1 patient was from the control group, 4 patients from the M group, and 9 patients from the M+B group, showing a significant increase in M+B group compared to the control group(Table3). There was no significant difference in other side effects including headache, postoperative nausea and vomiting (PONV), respiratory depression, somnolence, shivering, or hypotension. (p>0.05) (Table 3) Time to ambulation was comparable in all three groups (23.7±5.3hr in the control group vs 23.3±6.3hr in the M group vs 25.1±8.6hr in the M+B group) (p=0.267).

Table 3. Side effect of intrathecal injection for postoperative 3days

	Group Control	Group M	Group M+B	p
Headache	3(10.7%)	2(7.1%)	6(20.0%)	0.316
PONV	8(28.6%)	9(32.1%)	11(36.7%)	0.804
Pruritus	1(3.6%)	4(14.3%)	9(30.0%)*	0.023
Respiratory depression	0(0%)	0(0%)	0(0.0%)	
Somnolence	16(57.1%)	18(64.3%)	19(63.3%)	0.836
Hypotension	1(3.6%)	2(7.1%)	3(10.0%)	0.630
Tingling	0(0.0%)†	0(0.0%)†	6(20.0%)	0.010
Shivering	3(10.7%)	4(14.3%)	2(6.7%)	0.638

PONV: postoperative nausea and vomiting
The numbers are number of patients (percentage, %).
*p<0.01 vs. group Control
†p<0.05 vs. group M + B

Propofol and remifentanil requirement during surgery were comparable in the three groups (p=0.825, p=0.772 respectively) Intraoperative hemodynamic parameters, Table 4, show that there were no significant differences in HR, MBP, CVP, or BIS among the three groups during the operation. FloTrac indices also showed no significant differences in CI, SVV, or SVRI among the three groups (p>0.05) (Table4). Postoperative MBP showed no difference at 30 minutes upon arrival at the PACU (p=0.129) or at 60minutes upon arrival at the PACU (p=0.336).

Table 4. Intraoperative findings

	Group Control	Group M	Group M+B	p
HR (bpm)				
Initial	72.3±14.3	74.6±15.7	74.1±13.2	0.811
Induction	69.7±11.3	71.4±14.2	69.6±12.9	0.845
Skin incision	60.9±9.2	62.4±11.9	61.9±10.9	0.856
2 hours	69.5±13.1	68.2±11.9	69.8±11.2	0.865
3 hours	68.2±9.9	66.9±11.7	69.6±10.4	0.645
4 hours	72.2±11.4	70.5±12.9	73.6±9.8	0.669
End of surgery	78.2±19.0	71.8±15.1	78.0±15.2	0.249
MAP (mmHg)				
Initial	91.9±15.1	92.7±11.3	88.7±14.7	0.506
Induction	77.4±13.5	77.0±10.0	76.9±15.0	0.990
Skin incision	77.6±13.0	75.5±10.8	75.5±12.3	0.756
2 hours	88.6±10.2	86.0±9.9	88.6±10.4	0.545
3 hours	83.4±8.8	83.4±8.6	84.6±11.2	0.884
4 hours	85.8±10.3	79.7±11.1	85.1±10.7	0.144
End of surgery	93.2±14.8	85.5±11.5	91.6±15.3	0.102
CVP (cmH_20)				
Initial	-			
Induction	5.8±2.4	5.8±4.0	5.9±2.4	0.998
Skin incision	6.0±2.5	5.7±5.7	5.5±2.4	0.728
2 hours	5.2±2.0	4.9±2.3	4.1±2.9	0.272
3 hours	4.7±1.7	4.6±2.1	4.8±1.7	0.926
4 hours	5.0±1.5	4.5±2.4	4.9±2.0	0.759
End of surgery	6.0±2.3	6.0±2.8	5.9±2.3	0.978
BIS				
Initial	99.2±2.7	98.7±2.9	98.9±2.0	0.785
Induction	33.9±9.0	41.3±12.3	39.4±12.9	0.052

Skin incision	30.1±8.7	31.9±7.2	32.5±7.8	0.491
2 hours	29.4±7.3	30.2±6.0	31.6±7.0	0.470
3 hours	30.7±6.9	33.4±5.4	32±5.4	0.257
4 hours	34.4±6.0	34.2±6.9	34.8±5.3	0.955
End of surgery	41.8±12.0	40.5±10.7	38.5±9.0	0.491
GDFT[1]_CI≥2.0 (%)	78.9±29.0	86.3±20.8	86.5±17.9	0.464
GDFT_SVRI≤3000 (%)	95.8±11.9	97.3±7.7	99.5±1.9	0.113
GDFT_MAP≥75 (%)	86.8±14.0	76.0±21.9	78.9±19.6	0.055
GDFT_SVV≤13 (%)	87.9±17.6	76.7±27.4	82.3±24.7	0.190

[1]Goal directed fluid therapy was practiced in our study to maintain proper fluid management for our patients based on the following indices (SVV <13%, MAP > 75 mmHg, CI >= 2.0 L/min/m2, SVRI <= 3000 dynes•sec/cm5/m2). HR: heart rate, MAP: mean arterial pressure, CVP: central venous pressure, BIS: bispectral index score, GDFT: goal-directed fluid therapy, CI: cardiac index, SVRI: systemic vascular resistance index, SVV: stroke volume variation

IV. DISCUSSION

In this study, addition of low dose bupivacaine to intrathecal morphine failed to show supplementary analgesics benefits in comparison to intrathecal morphine injected singularly. We revealed that there were analgesic benefits of intrathecal morphine injection and intrathecal morphine with bupivacaine injection in comparison to the control group, but neither group superior to the other after liver resection. The patients reported significantly lower pain scores and overall opioid consumption was decreased via IV PCA in both intervention groups in comparison to the control group. Immediate postoperative pain control reflected by time to first rescue analgesic was not significantly superior in the bupivacaine with morphine group compared to the morphine group.

A relatively low dose of morphine (eg. <500mcg) with a local anesthetic regimen is suggested to provide the optimal analgesic benefits with decreased side effects in patients. However, the consensus for bupivacaine dosage is wanting. Lemoine et. al suggested that the optimal spinal dose of bupivacaine for the recovery of motor function and guaranteed hospital discharge in patients undergoing ambulatory surgery

was 7.5 mg as this dose resolved motor block within 5 h and achieved discharge within 6 h in 95% of patients.(17) However, Karamuz et al demonstrated that 7.5mg intrathecal bupivacaine resulted in higher incidences of side effects including hypotension and shivering compared to bupivacaine 4mg combined with fentanyl 25mcg which provided adequate anesthesia for transurethral prostatectomy.(18) Guidaityte et al. reported that intrathecal injection of 4mg and 5mg intrathecal bupivacaine provided sufficient anesthesia for anorectal surgery with a sensory block duration of 4 to 5 hours with a maximum VAS at 6 hours.(19) A higher dose of 7.5mg Intrathecal bupivacaine provided a longer duration of both sensory and motor block. Motamed et. Al showed that 5mg bupivacaine with morphine (75 or 100mcg) was effective in postoperative analgesia for elective laparoscopic cholecystectomy. (20) To our knowledge, no previous studies have been performed that investigate low dose bupivacaine with morphine against morphine in liver resection. To avoid further induction of side effects brought by a higher dose, 5mg was used in this study. Because an ideal analgesic method has maximal benefits with the lowest possible side effects, verifying the synergic effects of low dose bupivacaine with intrathecal morphine could enhance the recovery of major abdominal surgeries including liver resection.

Unfortunately, our study suggested that morphine injected intrathecally alone at a low dose of 400mcg is comparable to morphine combined with 5mg of bupivacaine, and there were no additional benefits.

Koning et. al investigated the use of 12.5mg bupivacaine with 300mcg morphine intrathecally in 150 patients undergoing robot-assisted radical prostatectomy.(14) They found a mean reduction in less IV opioids during admission and lower pain scores, which was reflected in our study as well. An increase of bupivacaine dosage may provide additional analgesic effects; however, a higher dose of intrathecal bupivacaine may also induce unwanted hemodynamic disturbances and undesired side effects such as tingling sensation, sensory and motor block. Increasing the dosage

of bupivacaine may warrant a further decrease in perioperative blood pressure causing episodes of hypotension that require intervention. Although previous studies investigated a higher dosage of bupivacaine as an additive without further unwanted hemodynamic side effects, different factors may aggravate hemodynamic disturbances such as age, hypovolemia, and possibly the difference of race. Especially in the case of hepatectomy, intraoperative restrictive fluid management is often required which predisposes a higher risk for hypotension and a deeper sympathetic block for postoperative pain management may aggravate this risk.(20) When increasing the dose of bupivacaine for liver resection, this should be taken into consideration, carefully weighing the risk and benefits. It is necessary to meticulously adjust the dosage of additive bupivacaine and further studies are warranted to evaluate optimal dosage of local anesthetic additive to intrathecal morphine.

Pruritus was increased in both intervention groups, which was in accordance with other studies. Prophylactic drugs against pruritus including ondansetron and dehydrobenzperidol were not administered in this study. Including a prophylactic measure and continuation of 5-HT_3 antagonists may have decreased incidence of pruritus in the intervention groups.

Respiratory depression was not present in this study. Studies that report late onset respiratory depression that required intervention due to intrathecal morphine usually presented cases with higher dose morphine (>500mcg).(21) Clinically relevant respiratory depression is shown unlikely to occur with lower doses of intrathecal morphine and thereby, we did not institute specific monitoring for respiratory depression overnight.

Although there are a variety of possible analgesic methods including peripheral nerve blocks for hepatectomy to achieve multimodal analgesia, intrathecal injection is a relatively easier method to perform in the clinical field. Thereby, it is important to assess the additive or synergic analgesic effects of bupivacaine to find the optimal dose. However, because it is suggested that a higher dose may bring further unwanted

side effects, further studies should take this into consideration and carefully weigh the risk and benefits. Other intrathecal regimens should also be taken into consideration for postoperative pain control after liver resection. Alpha 2 adrenoreceptor antagonists including clonidine and dexmedetomidine are increasingly being acknowledged as a local anesthetic adjuvant. Crespo et. al suggested that intrathecal clonidine a safe adjuvant to neuraxial anesthesia in prolonging sensory block and motor block without increasing hypotension, pruritus, or PONV. Other drugs including ketamine and steroids have been used with mixed results.(22) However, these regimens require further research in regards to the safety profile.

This study has limitations. First, because this study was performed in a single center institution with a small sample size, there is a disadvantage of the lack of generalizability. Secondly, this study evaluated a single dose of bupivacaine. Further studies may be needed to identify optimal regimen for hepatectomy.

V. CONCLUSION

Intrathecal morphine can be effectively implemented in a multimodal analgesic approach in reducing overall opioid consumption in the postoperative care of liver resection in the first 24 hours. Addition of 5mg bupivacaine may be insufficient to provide analgesic benefits in combination with intrathecal morphine, but result in sensory and motor block and tingling sensation in the case of hepatectomy. Therefore, intrathecal analgesia may warrant additional study for optimal regimen.

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ABSTRACT (IN KOREAN)

Analgesic effect of intrathecal morphine combined with low dose bupivacaine on postoperative analgesia after liver resection: A randomized, controlled preliminary study

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목적: 효과적인 통증 조절은 수술 후 환자의 관리에 중요한 역할을 한다. 간 절제술 후 통증 조절을 위한 multimodal approach 중 하나로 척수강내 morphine 투여가 사용되어 왔다. 그러나 고용량의 부피바카인은 의도하지 않게 원치 않는 부작용을 일으킬 수 있다. 이 연구의 목적은 척수강 내 모르핀 주사와 저용량 부피바카인의 효과를 모르핀 주사와 비교하고자 한다.

방법: 간절제술을 받는 환자들을 세 군으로 나누었다. 각 환자는 군 배정에 따라 전신 마취 유도 직전에 다음과 같이 procedure 를 받았다 (1) 대조군은 subQ 에 sham injection; (2) 모르핀 군(M)은 모르핀 400mg; (3) 모르핀 및 부피바카인 군(M+B)의 경우 모르핀 400mcg 및 부피바카인 5mg. 주요 결과는 first rescue analgesia 시간이며 VAS(visual analogue scale) 통증 점수는 postoperative day(POD) 1 까지 비교했다. 환자 조절 진통제에 의해 투여된 총 펜타닐 용량은 POD2 까지 기록되었다. 잔류 효과에 대해 POD 3 까지 부작용을 모니터링했다.

결과: First rescue analgesia 까지 M 군과 M+B 군에 비해 대조군에서 유의하게 짧았으나 ($p<0.001$) 두 군은 서로 비슷했다. 대조군에 비해 M 군과 M+B 군에서 VAS 점수와 PCA(환자 조절 진통제)를 통한 총 펜타닐 투여가 유의하게 감소했지만 중재군 간에 차이는 없었다. 대조군은 M 군 및 M+B 군에 비해 더 많은 진통제가 필요했다. 그러나 M 군과 M+B 군 간에는 차이가 없었다. 가려움증은 대조군에 비해 M+B 군에서 더 많았고($p=0.023$), 저림은 다른 군에 비해 M+B 군에서 유의하게 높았다($p=0.010$).

결론: 5mg 의 부피바카인을 추가하는 것은 추가 진통 효과를 제공하는 데 충분하지 않을 수 있다. 그러나 고용량의 부피바카인은 부작용을 악화시킬 수 있다. 합병증에 대한 수술 후 통증 조절을 위한 최적의 요법을 조사하기 위한 추가 연구가 필요하다.

핵심되는 말: intrathecal, bupivacaine, analgesia