Nausea, Vomiting and Pruritus Induced by Intrathecal Morphine

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Background: *Presently, in Siriraj Hospital, intrathecal morphine is routinely used in spinal anesthesia for postoperative pain control in more than 600 cases per month with doses lower than 0.3 mg. However, the incidence of side effects is high. This retrospective data review was performed to identify incidence and risk factors of postoperative nausea, vomiting, and pruritus.*
Material and Method: *One thousand three hundred six anesthetic records were analyzed for incidence of nausea, vomiting, and pruritus after spinal anesthesia with intrathecal morphine in Siriraj Hospital between October 2010 and April 2011. Data extracted were age, gender, type of operations, dosage of spinal morphine, and frequency, and severity of adverse effects (nausea, vomiting, and pruritus). Odd ratios and multiple logistic regression analysis were used.*
Results: *Incidence of nausea, vomiting, and pruritus were 21.5, 14.8, and 59.5% respectively. No respiratory depression and urinary retention was reported. There was statistically significant correlation in the incidence of nausea, vomiting, and pruritus with female gender, cesarean section, and intrathecal morphine dose ($p<0.001$). Intrathecal morphine more than 0.2 mg resulted in an increase in severity of side effects.*
Conclusion: *The intrathecal morphine is effective in postoperative pain control. However, it induces high incidence of nausea, vomiting, and pruritus. Prevention of side effects and alternatives to intrathecal morphine need further research.*

Keywords: *Intrathecal morphine, Nausea, Vomiting, Pruritus*

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Since 1979, intrathecal morphine has been effectively used for postoperative pain management[1]. The dose has been purposively reduced to the range of 0.1 to 0.25 mg for providing both effective analgesia and low side effects and complication[2-4]. In 2009, M. Gehling and M. Tryba did a meta-analysis of risks and side effects of intrathecal morphine combined with spinal anesthesia[5]. The study concluded that even low dose intrathecal morphine (less than 0.3 mg) is accompanied by nausea (RR 1.4, 95% CI 1.1-1.7), vomiting (RR 3.1, 95% CI 1.5-6.4), and pruritus (RR 1.8, 95% CI 1.4-2.9) compared to placebo. However, increasing the morphine dose did not increase the incidence of side effects. At present, in Siriraj Hospital, intrathecal morphine with spinal anesthesia is routinely used for postoperative pain control in more than 600 cases a month with a dose lower than 0.3 mg for prevention of respiratory depression.

This retrospective anesthetic and post-operative record review was performed to identify incidence and risk factors of nausea, vomiting, and pruritus induced by intrathecal morphine.

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Material and Method

After approval of the institutional ethic committee, this retrospective descriptive study was conducted by reviewing all medical record of surgical patients who received spinal anesthesia between October 2010 and April 2011. We recruited only patients who were interviewed by a postoperative care nurse within 24 hours postoperatively and all side-effect data were recorded. We excluded patients who received different intrathecal opioid, dose of intrathecal morphine more than 0.3 mg, and when spinal anesthesia was used in combination with

general anesthesia. Data extracted were age, gender, weight, height, ASA classification, type of operations, amount of spinal morphine, incidence and severity of nausea, vomiting, pruritus, and respiratory depression.

Statistical analysis

Data were processed using SPSS for Windows (Statistical Package for the Social Science) version 13.0. Ordinary data such as age and BMI were analyzed by mean and standard deviation. The risk factors were identified by Univariate analysis. If p-values were <0.05 risk factors were analyzed by multiple logistic regression and presented by adjusted odds ratio (OR) and 95% confidence interval (95% CI). The p-value of <0.05 was considered statistically significant.

Results

One thousand three hundred six patients' data were reviewed. Seventy-eight patients who received general anesthesia combined with spinal block and 72 patients who received intrathecal fentanyl were excluded. Therefore, 1,156 patients were included in final analysis and 843 patients had intrathecal morphine for postoperative pain control.

There were 258 male (22.3%) and 898 female (77.7%) patients, mean age was 42.3±0.52 (range 18-93) years, weight 66.3±0.37(range 38-127) kg, and height 159.23±0.23 (range 152-190) cm. Risk score (ASA) of the patients was mostly ASAI and II (n = 1,077). The surgical procedures and characteristics of spinal anesthesia are shown in Table 1.

Overall incidence of nausea, vomiting, and pruritus were 18.2%, 12.0%, and 44.1% respectively. Adding morphine intrathecally increased the incidence of nausea from 9.3% to 21.5% postoperatively in the risk ratio of 2.7 with 95% CI of 1.8, 4.1, p<0.001 (Table 2). Intrathecal morphine also significantly increased the incidence of vomiting from 4.5% to 14.8% (odds ratio 3.7, p<0.01, 95% CI 2.1, 6.6), and pruritus from 2.6% to 59.5% (odds ratio 56.1, p<0.001, 95% CI 27.4, 114.8).

Patients with intrathecal morphine (n = 843), mostly received equal to or lower than 0.2 mg (n = 763; 90.5%), whereas 80 (9.5%) received more than 0.2 mg. The incidence of postoperative nausea was significantly increased in dose of intrathecal morphine was more than 0.2 mg. However, the incidence of vomiting and pruritus between these two groups was not statistically different (Table 3) but the side effects were significantly more severe in patients with high morphine dose (Table 4).

Statistical analysis revealed female gender as a significant risk factor for nausea, vomiting, and pruritus. Age more than 30 years significantly increased the incidence of nausea but decreased the incidence of pruritus. Operation of lower abdomen and cesarean section were significantly associated with the incidence of pruritus (Table 5).

Table 1. Type of operations and drugs used for spinal anesthesia

Variables	Cases (n = 1,156)	Percentage
Operation		
Cesarean section	582	50.3
Lower limb	235	20.3
Lower abdomen	208	18.0
Perineum	131	11.3
Local anesthetic agents for spinal anesthesia		
Heavy bupivacaine	1,080	93.4
Isobaric bupivacaine	76	6.6
Spinal morphine		
No	313	27.1
Yes ≤0.2 mg	763	66.0
Yes >0.2 mg	80	6.9

Table 2. Incidence (percentage) of nausea, vomiting and pruritus compared between patient received spinal anesthesia (n = 1,156) with or without intrathecal morphine

Intrathecal morphine	Nausea (%)	p-value	Odds ratio	95% CI
Total cases	18.2			
Morphine				
No	9.3	<0.001	2.7	1.8, 4.1
Yes	21.5			
	Vomiting (%)			
Total cases	12.0			
Morphine				
No	4.5	<0.001	3.7	2.1, 6.6
Yes	14.8			
	Pruritus (%)			
Total cases	44.1			
Morphine				
No	2.6	<0.001	56.1	27.4, 114.8
Yes	59.5			

Using stepwise multiple logistic regression analysis (Table 6), we found out that the incidence of nausea was significantly associated with female gender (OR 2.99, 95% CI 1.66, 5.42, p-value <0.001), cesarean section (1/OR = 4.17, 95% CI 2.08, 8.34, p-value <0.001), and intrathecal morphine (OR 3.78, 95% CI 2.19, 6.81, p-value <0.001). Incidence of vomiting and pruritus were also significantly associated with female gender, cesarean section, and intrathecal morphine.

Table 3. The incidence of nausea, vomiting and pruritus comparing between intrathecal morphine equal to or lower than 0.2 mg. and more than 0.2 mg

Intrathecal morphine (mg)	Nausea	Vomiting	Pruritus
≤0.2 (n = 763)	19.6%	14.3%	58.6%
>0.2 (n = 80)	31.3%	20.0%	68.8%
	p = 0.015 OR = 1.9 95% CI 1.1, 3.1	p = 0.18 OR = 1.5 95% CI 0.8, 2.7	p = 0.09 OR = 1.5 95% CI 0.9, 2.5

Table 4. Severity of nausea, vomiting and pruritus comparing between intrathecal morphine of lower or equal to 0.2 mg and more than 0.2 mg

Severity	Dose spinal morphine		p-value
	≤0.2 mg	>0.2 mg	
Nausea			
None	614 (80.5%)	55 (68.8%)	0.03
Improve by treatment	144 (18.9%)	25 (31.3%)	
Not improve	5 (0.7%)	0	
Vomiting			
None	653 (85.7%)	64 (80.0%)	0.03
<3/day	91 (11.9%)	11 (13.8%)	
≤3-5/day	18 (2.4%)	5 (6.3%)	
Pruritus			
No	315 (41.3%)	25 (31.3%)	0.006
Yes			
No treatment	383 (50.3%)	40 (50.0%)	
Needed treatment	64 (8.4%)	15 (18.8%)	

Table 5. Comparative incidence of nausea, vomiting and pruritus between sex, age and group of operation after spinal anesthesia

Variables	Nausea		Vomiting		Pruritus	
	Percent	Stat analysis	Percent	Stat analysis	Percent	Stat analysis
Sex						
Male	8.1	p<0.001	5.0	p<0.001	6.6	p<0.001
Female	79.0	OR = 3 95% CI 1.9, 4.8	14.0	OR = 3.1 95% CI 1.7, 5.5	54.9	OR = 17.3 95% CI 10.4, 28.4
Age						
<30 yr	14.2	p = 0.04	8.9	p = 0.06	54.3	p<0.001
>30 yr	19.6	OR = 1.5 95% CI 1.0, 2.1	13.1	OR = 1.5 95% CI 1.0, 2.4	40.5	OR = 3 95% CI 1.9, 4.8
Operation						
Lower limb and perineum	18.6	p = 0.8	13.8	p = 0.2	17.8	p<0.001
C/S and lower abdomen	18.0	OR = 1 95% CI 0.8, 1.3	11.2	OR = 0.8 95% CI 0.5, 1.1	56.9	OR = 6.1 95% CI 4.5, 8.2

Table 6. Multiple logistic regression analysis risk factor of nausea, vomiting and pruritus after spinal anesthesia

Variables	Nausea		Vomiting		Pruritus	
	Adjusted OR	95% CI p-value	Adjusted OR	95% CI p-value	Adjusted OR	95% CI p-value
Female	2.99	1.66, 5.42 <0.001	2.72	1.32, 5.61 0.01	2.78	1.37, 5.64 0.01
Cesarean section	4.17	2.08, 8.34 <0.001	7.14	3.13, 16.67 <0.001	2.24	0.93, 5.37 0.07
Lower limb	1.31	0.69, 2.50 0.41	1.18	0.55, 2.52 0.68	3.55	1.43, 8.86 0.01
Lower abdomen	0.91	0.45, 1.86 0.79	0.64	0.28, 1.46 0.29	3.37	1.34, 8.46 0.01
Intrathecal morphine	3.86	2.19, 6.81 <0.001	7.37	3.63, 14.95 <0.001	30.9	13.8, 69.33 <0.001

Discussion

In our study nausea, vomiting, and pruritus turned out to be common side effects after spinal anesthesia. Following multiple logistic regression analysis the incidence of nausea and vomiting were significantly related to female gender, caesarian section, and intrathecal morphine. Incidence of pruritus was significantly related to female gender and intrathecal morphine. The finding of our study is similar to Gwirtz et al[6], who found an incidence of nausea and vomiting of 25% in 5,969 patients. Malinee et al[7] studied post-operative analgesia after intrathecal morphine injection combined with patient-controlled analgesia (PCA) in 260 patients. They reported an incidence of nausea and vomiting of 24%. Furthermore, 1.5% of patients did not improve after receiving treatment. Intrathecal morphine was the only manageable factor that significantly increased the incidence of nausea in the adjusted OR of 3.86 (95% CI 2.19, 6.81), vomiting in the adjusted OR of 7.37 (95% CI 3.63, 14.95), and pruritus in the adjusted OR of 30.9 (95% CI 13.8, 69.33).

In our study, the most frequent side effect was pruritus with an incidence of 59.5%, being higher than reported by Gwirtz et al and Malinee et al with 37% and 19.1%, respectively. The high incidence in our study may result from patients characteristics, 50.3% undergoing cesarean section, as the incidence of pruritus in cesarean section is 6.1 times higher than other types of surgery. Somrat et al[8] studied the prevention of pruritus in 240 patients who had spinal block with intrathecal morphine undergoing Cesarean section. Incidence of pruritus was 94%.

The difference of incidence may result from method of study. In the present study, patients were asked only once in the first 24 hours postoperatively. However, if the patients would have been asked frequently, the incidence of pruritus would be higher.

In our practice in Siriraj Hospital, the dose of intrathecal morphine usually is not more than 0.3 mg to avoid respiratory depression but provide adequate pain control. Higher doses of intrathecal morphine significantly increased the severity and incidence of nausea but only the severity of vomiting and pruritus. Research in both volunteers[12] and postoperative patients[10] has suggested that the incidence of nausea and vomiting after intrathecal morphine was dose-related. Our findings have a similar tendency. However, Nortcliffe et al[9] used 0.1 or 0.2 mg spinal morphine for analgesia in cesarean delivery and observed 67% and 60% incidence rates of nausea and vomiting respectively, which does not confirm the incidence of nausea and vomiting after intrathecal morphine as being dose related[10]. Nausea and vomiting have also had been reported in cesarean delivery parturients who did not receive intrathecal morphine. This is an indication that the surgical procedure itself has a strong influence on these side effects[11].

Female gender was a significant risk factors for nausea, vomiting, and pruritus after spinal anesthesia. These results are similar to Noppamas et al[13], who reported a higher incidence of side effects in female patients.

Pruritus is extremely inconvenient for patients and its prevention, though it seems to be difficult[14], should have a high impact on practice guidelines.

Conclusion

Intrathecal morphine is effective in post-

operative pain control. However, even in a low dose (≤0.2 mg), it frequently causes highly discomforting side effects, such as nausea, vomiting, and pruritus. Future studies should focus on attenuating side effects of intrathecal morphine and alternative methods for postoperative pain control.

Potential conflicts of interest

None.

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อุบัติการณ์ผลข้างเคียงจากการฉีดมอร์ฟีนเข้าช่องไขสันหลัง

ฐิติมา ชินะโชติ, ปวริศร นิลรัตน์, ปิยะภัทร สมานพิบูลย์ผล

ภูมิหลัง: *ปัจจุบันผู้ป่วยที่ได้รับการระงับความรู้สึกด้วยวิธีการฉีดยาชาเฉพาะที่เข้าในช่องไขสันหลังเพื่อการผ่าตัด จะได้รับมอร์ฟีนในปริมาณน้อยกว่า 0.3 มก. ร่วมด้วยเพื่อควบคุมอาการปวดหลังการผ่าตัด ในโรงพยาบาลศิริราชเป็นเทคนิคที่ได้รับการเลือกใช้มากกว่าเดือนละ 600 ราย ซึ่งตรวจพบอาการคลื่นไส้ อาเจียน อาการคัน ค่อนข้างมาก จึงดำเนินการศึกษาเพื่อค้นหาอุบัติการณ์และปัจจัยเสี่ยงของอาการดังกล่าว*

วัสดุและวิธีการ: *โดยศึกษาจากรายงานการให้ยาระงับความรู้สึกและบันทึกการตรวจเยี่ยมหลังการผ่าตัด ในผู้ป่วย 1,306 ราย ที่ได้รับการระงับความรู้สึกด้วยวิธีการฉีดยาชาเฉพาะที่เข้าในช่องไขสันหลัง ระหว่างเดือนตุลาคม พ.ศ. 2553 ถึง เมษายน พ.ศ. 2554 ทำการบันทึกรายละเอียดผู้ป่วย การผ่าตัด ปริมาณมอร์ฟีนที่ได้รับ อาการคลื่นไส้ อาเจียน และอาการคัน และความรุนแรงของอาการดังกล่าว ในระยะหลังการผ่าตัด*

ผลการศึกษา: *การฉีดมอร์ฟีนเข้าในช่องไขสันหลังทำให้เกิดอาการคลื่นไส้ อาเจียน อาการคัน 18.2, 12 และ 41.1% ตามลำดับ ไม่พบรายงานภาวการณ์กดการหายใจ ภาวะข้างเคียงดังกล่าวสัมพันธ์กับเพศหญิง การผ่าตัดคลอดลูก และปริมาณมอร์ฟีนที่ได้รับอย่างมีนัยสำคัญทางสถิติ ปริมาณมอร์ฟีนที่มากกว่า 0.2 มก. จะเพิ่มความรุนแรงของผลข้างเคียงดังกล่าว*

สรุป: *แม้ว่าการให้มอร์ฟีนทางช่องไขสันหลังช่วยในการระงับปวดหลังการผ่าตัดได้อย่างดี แต่ก็เป็นปัจจัยที่เพิ่มอุบัติการณ์ผลข้างเคียงด้านอาการคลื่นไส้ อาเจียน และอาการคันในระดับสูง ควรดำเนินการศึกษาต่อเนื่องเพื่อลดอุบัติการณ์ และเพิ่มความพึงพอใจของผู้ป่วย*