

# *Morinda Citrifolia* Linn. for Prevention of Postoperative Nausea and Vomiting

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**Objective:** To be a preliminary, prospective, randomized, double blinded, placebo-controlled trial to evaluate the efficacy of *Morinda citrifolia* Linn or noni for the prevention of postoperative nausea and vomiting (PONV) in patients considered high risk for PONV after various types of surgery.

**Material and Method:** The plant extract was prepared by boiling of dried noni fruit (maturity stage 3-4) then evaporated under standard procedure and processed into capsules. The doses were 150mg, 300 mg and 600 mg which are equivalent to 5, 10 and 20 g of dried noni fruit, respectively. One hundred patients of ASA physical status I or II, aged 18-65 years, and considered at risk for PONV, were randomized to receive 150, 300, 600 mg of noni extract or a placebo orally 1 hours before surgery. Standard general anesthetic technique and postoperative analgesia were employed.

**Results:** Significantly fewer patients who had received the 600 mg noni extract experienced nausea during the first 6 hours compared to the placebo group (48% for the 600mg noni group and 80% for the placebo group, p-value = 0.04). The incidence of PONV in other time periods was not statistically different for all three noni doses compared to the placebo group. No side effects were reported in all groups.

**Conclusion:** *Morinda citrifolia* Linn. has an antiemetic property and prophylactic noni extract at 600 mg (equivalent to 20g of dried noni fruit or scopoletin 8.712 µg) effectively reduces the incidence of early postoperative nausea (0-6 hours).

**Keywords:** *Morinda citrifolia*, Noni, Antiemetics, Emesis, Thai Traditional Medicine, Anesthesia

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Postoperative nausea and vomiting (PONV) is one of the most common side effects associated with surgery and anesthesia. In multiple surveys, patients listed the avoidance of PONV as the number one priority when faced with surgery and anesthesia; interestingly this issue ranks ahead of the concern of postoperative pain. In addition to medical consequences of PONV, patient satisfaction is closely associated with the effectiveness of PONV avoidance<sup>(1-4)</sup>. Aggressive prophylaxis is costly; however it is justified in high risk patients<sup>(5)</sup>. Clearly this is a problem worth addressing, and a great deal of time, money and effort is spent each year dealing with the prevention and treatment of PONV.

In traditional medicine, certain herbs, such as *Morinda citrifolia* Linn, are advocated as beneficial

for prevention and treatment of nausea and vomiting. *Morinda citrifolia* Linn., also known as noni fruit or “yor” in Thai, has been used for food and for medical purposes for more than one thousand years<sup>(6)</sup>. It has been claimed in Traditional Thai Pharmacopeias that hot water extract of dried ripe noni fruit has an antiemetic property, and frequent sips of the extract can help relieve the symptom of nausea and vomiting<sup>(7,8)</sup>.

Commercial interest in noni has been established worldwide, as evidenced by the number of patents registered in recent years. Dried grounded noni fruit powder has been available in worldwide markets and advertised as having multiple uses including the antiemetic property. However, despite the real market opportunities, there has never been scientific research of the antiemetic effect of this product.

This preliminary study was primarily aimed to evaluate the potential of noni fruit extract to prevent nausea and vomiting in postoperative patients who were at risk. Secondary objectives were to determine

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the optimal dose of the extract for PONV prophylaxis, and to indicate other potential benefits as well as undesirable side effects of its use for prevention of PONV.

### **Material and Method**

The Thammasat University Research Ethical Committee approved this study and all patients gave their written informed consent. One hundred surgical patients, aged 18-65 years, who were healthy or had controlled systemic disease and were to undergo elective surgery under general anesthesia, and who also had at least 3 of 4 predictors of PONV (female gender, history of PONV, non-smoking, and opioid use), were randomly selected for this double blinded, placebo controlled trial. Exclusion criteria ensured there were no patients who received antiemetics within 24 hours, had a full stomach, underwent neurological/bowel surgery, did not expect to extubate after surgery, had potential morbidity associated with PONV or had hyperkalemia.

Eligible patients were allocated randomly to one of 4 groups to receive a placebo (P group), 150 mg of *Morinda citrifolia* Linn (noni) extract, which is equivalent to 5 g of dried noni fruit (M1 group), 300 mg of noni extract, which is equivalent to 10 g of dried noni fruit (M2 group), and 600 mg of noni extract which is equivalent to 20 g of dried noni fruit (M3 group) in the form of two identical capsules taken orally with a sip of water 1 hour before surgery. The random allocation was based on a computer generated number with the assignment being kept in a concealed envelope until the time of administration. All patients underwent standardized anesthetic protocol. General anesthesia with endotracheal tube was performed using similar anesthetic agents including thiopental/propofol as an induction agent, maintained level of anesthesia with inhaled anesthetic (isoflurane/sevoflurane), muscle relaxant, and strong opioids (morphine fentanyl). Every case received reversal agents for residual muscle relaxant. No antiemetics were administered preoperatively or during anesthesia. Regular post-operative pain control with morphine was employed using the patient controlled analgesia (PCA) technique.

All episodes and severity of nausea, vomiting, use of rescue antiemetics were recorded within the first 24 hours postoperatively, divided into 2 time periods of 0-6 hours as early postoperative period and 6-24 hours as delayed postoperative period. PONV was evaluated by specially trained anesthetist nurses who were unaware of the drug given to the patients.

Nausea was defined as subjectively unpleasant sensation represented by an awareness of the urge to vomit. Vomiting or emesis was defined as the forceful expulsion of GI content to the mouth. This present study, the authors considered retching in the same group as vomiting. The severity of nausea was graded using a numeric scoring system ranging from 0 (no nausea) to 10 (the worst possible). Severity of vomiting was recorded as number of vomiting episodes; all episodes that lapsed less than 1 minute were counted as 1 episode. Patients received initial rescue treatment immediately in response to the first emetic episode or patient request as a result of nausea. Rescue antiemetic was 4 mg of ondansetron administered intravenously every 6 hours and 0.2 mg/kg of metoclopramide was added if the symptom persisted. Morphine consumption, undesirable side effects were recorded. Patients' satisfaction with PONV management was evaluated using a numeric scoring system.

The sample size was predetermined. A power analysis was based on the assumption that the estimated incidence of PONV in the placebo group would be 60%. A reduction from 60% to 30% was considered clinically significant. Since 95% CI of 30% is approximately 20-40% and this is a preliminary study, the investigators calculated sample size based on the reduction of PONV incidence to 20% with 5% type one error ( $\alpha=0.05$ ) and a power ( $1-\beta$ ) of 80%. The sample size of 25 patients was needed for each group. The analyses of data were performed by the following statistical methods. Patient characteristics were analyzed by one-way ANOVA and Chi-square. The number of patients who had nausea, vomiting, and use of rescue antiemetic were compared pairwise to the placebo group using Chi-square test. Patients' satisfaction was compared using Kruskal-Wallis test. A two-sided significance level of 0.05 was used for all analyses.

### **Preparation of noni extract**

#### **Plant Material**

Noni fruits in maturity stage 3-4 (pale yellow, very hard to fairly hard) were collected from the same source at the same time in Thailand. The noni fruits were washed with water, air dried and placed in an oven to dry at 50°C and powdered in an electrical blender.

#### **Extraction**

Noni powder was boiled with distilled water for 15 minutes. The mixture was filtered and the clear residue was evaporated at 60-70°C by a Rota evaporator.

The filtrate was boiled and processed with the same method again 3 times. Then all the aqueous extract was collected and dried by vacuum drier.

#### **Phytochemical detection and capsulation**

The extract was analyzed to determine the amount of the extract that was derived from 5 g of dried noni fruit, and then calculated to determine the amount of extract derived from dried noni 10 and 20 g. The extract was analyzed using the HPLC technique to determine the amount of noni marker (scopoletin). There was approximately 0.0116 µg/mg of scopoletin in the extract. The extract was then diluted with lactose as needed to process the three selected study doses (150 mg, 300 mg and 600 mg of noni extract which are equivalent to 5, 10 and 20 g of dried noni respectively) and filled in identical capsules used for the study.

However, preparation of small amounts of extract and diluted with lactose may cause inhomogeneous of the extract in the study capsules. Three capsules from each of the three different dose groups were therefore randomly analyzed again at the end of the study, using the HPLC technique to determine the amount of noni marker (scopoletin) in the three different doses of the extract, which revealed 1.716 mcg of scopoletin/150 mg of extract dose, 4.786 mcg/300 mg of extract dose and 8.712 mcg/600 mg of

extract dose which ideally should all be equal to 0.0116 mcg/mg in every group.

The placebo was prepared by using lactose to fill identical capsules.

#### **Results**

One hundred surgical patients were studied, with 25 assigned to each group. No patient was excluded or unable to participate in the study. There were no significant differences between groups in patient demographics and operative characteristics (Table 1).

The overall incidence of PONV in the placebo group was 84% for nausea and 48% for vomiting in 0-24 hours. Significantly fewer patients in M3 (600 mg of noni extract) prophylaxis group experienced nausea at the first 6 hours compared to the placebo group, 48% versus 80% in M3 and placebo group respectively, p-value = 0.04. The incidence of PONV at other time periods was not statistically different (Table 2).

No undesirable side effects were observed in all study groups. Morphine consumption, time to start dietary intake and satisfaction with PONV management were not significantly different between groups.

#### **Discussion**

In general 20-35% of surgical patients experience PONV, which higher incidence up to 70-80%

**Table 1** Demographic Data

Data	Placebo (n = 25)	M1 (n = 25)	M2 (n = 25)	M3 (n = 25)
Age (year)	40 ± 7	41 ± 9	40 ± 10	36 ± 10
Weight (kg)	56 ± 13	57 ± 13	57 ± 8	57 ± 13
Female gender	23	24	22	24
History PONV	11	10	8	8
Anesthesia time (minute)	133 ± 62	146 ± 52	170 ± 68	150 ± 77
Type of surgery				
Laparoscopic gynecology	6	4	5	6
Gynecologic surgery	11	12	10	12
General surgery	3	3	4	2
Laparoscopic general surgery	4	4	4	4
Orthopedics	1	0	2	0
Eye/ENT surgery	0	2	0	1
Morphine consumption (mg)	26 ± 14	27 ± 13	24 ± 12	26 ± 14
Time to dietary intake (hour)	23 ± 5	21 ± 9	20 ± 5	21 ± 8

Values are mean ± SD or number in the group

M1 = 150 mg of morinda citrifolia extract, M2 = 300 mg of morinda citrifolia extract, M3 = 600 mg of morinda citrifolia extract

**Table 2.** Postoperative Nausea Vomiting

	placebo	M1	p-value	M2	p-value	M3	p-value
	(n = 25)	(n = 25)		(n = 25)		(n = 25)	
Postoperative 0-6 h							
Nausea	20 (80)	15 (60)	0.22	17 (68)	0.52	12 (48)	0.04*
Vomiting	9 (36)	10 (40)	1.00	10 (40)	1.00	6 (24)	0.54
Postoperative 6-24 h							
Nausea	15 (60)	15 (60)	1.00	13 (52)	0.77	15 (60)	1.00
Vomiting	9 (36)	7 (28)	0.76	8 (32)	1.00	8 (32)	0.54
Postoperative 0-24 h							
Nausea	21 (84)	19 (76)	0.73	18 (72)	0.50	16 (64)	0.20
Vomiting	12 (48)	12 (48)	1.00	14 (56)	0.78	10 (40)	0.77

Value are number (%), p-value compared to placebo \*p < 0.05

associated with numbers of factors. Patient-specific risk factors have been shown to be clinical relevant, therefore, prediction of a patient's risk independent of the type of surgery can be included in the calculation of simplified risk scores<sup>(4,9)</sup>. Christian et al found predictors of PONV were female gender, history of motion sickness or PONV, not smoking and opioid use. If none, one, two, three or four predictors were present, the incidence of PONV was 10%, 21%, 39%, 61% and 79%, respectively<sup>(9)</sup>. We controlled the factors within our study design by including patients with at least 3 of 4 predictors. The similar anesthetic technique and agents were employed. The duration of anesthesia and types of surgery were comparable among groups. Patients, anesthesia team in the operating room and anesthetist nurses who evaluated the patients postoperatively were unaware of the drug received. Therefore the difference in the occurrence of PONV among groups can be attributed to the difference in the study drugs.

Our study showed that a 600 mg dose of noni extract, derived from 20 mg of dried noni fruit and equivalent to approximately 8.712 mcg of noni marker (scopoletin) can lower the incidence of nausea in the early postoperative period. Unfortunately, it was the highest dose in this preliminary study. Optimal dose for PONV prevention, therefore, can not be determined but should not be less than 20 mg of dried noni fruit. This study confirmed, in a clinical setting, the existence of an antiemetic property of *Morinda citrifolia* Linn, which has not been established in scientific research. However, this property seems to be mild and appears to last no more than 6 hours. The extraction techniques

that allow increased concentrations and the ability to ensure sustained release of the active ingredients should be considered as an important role in the development of noni for clinical use in a PONV setting. The use of noni for nausea and vomiting from other causes which are less emetogenic may be possible, since general anesthesia with inhaled anesthetics and opioid based techniques is considered a strong emetogenic.

This study has some potential limitations. Since the compounds which possess the antiemetic activity in noni have not been clearly identified, we used scopoletin as a marker to detect the amount of noni in the extract, and this may not accurately approximate the actual active compounds with antiemetic properties in the noni extract. However, the extraction method imitated the method of extraction in Thai traditional pharmacopoeia which has been used for antiemetic purpose in traditional Thai medicine.

In conclusion, this study has demonstrated the antiemetic property of *Morinda citrifolia* Linn. The 600mg dose of noni extract (equivalent to 20 g of dried noni fruit/ 8.712mcg of scopoletin) was the minimum dose that effectively reduced the incidence of postoperative nausea in the early postoperative period. Further investigation is required to ascertain both the optimal dose and the active compounds of *Morinda citrifolia* Linn. for prevention of nausea and vomiting.

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## ผลยอสกัดใช้ป้องกันการคลื่นไส้อาเจียนหลังการผ่าตัด

สุนิสา ประไพตระกูล, อรุณพร อธิรัตน์

**วัตถุประสงค์:** เพื่อทดสอบหาประสิทธิภาพในการป้องกันอาการคลื่นไส้ และอาเจียนหลังการผ่าตัดในผู้ป่วย (PONV) ด้วยสารสกัด ลูกยอ (*Morinda citrifolia* Linn) โดยวิธีการศึกษาเบื้องต้นแบบไปข้างหน้า สุ่มแบบ double blinded โดยมีกลุ่มควบคุมคือยาหลอก

**วัสดุและวิธีการ:** ลูกยอสกัดโดยการต้ม และทำให้แห้งภายใต้กระบวนการผลิตแคปซูลมาตรฐานให้มีความเข้มข้น 150, 300 และ 600 มิลลิกรัม ซึ่งเทียบเท่ากับน้ำหนักแห้งของลูกยอที่ 5, 10 และ 20 กรัม ตามลำดับ โดยการสุ่มให้ผู้ป่วยจำนวน 100 คน ซึ่งอยู่ในภาวะเสี่ยงต่ออาการคลื่นไส้ และอาเจียนหลังการผ่าตัด รับประทานแคปซูลสารสกัดลูกยอขนาดต่าง ๆ ก่อนการผ่าตัดเป็นเวลา 1 ชั่วโมง โดยวิธีการมาตรฐาน

**ผลการศึกษา:** พบว่าภายหลังจากรับประทานสารสกัดลูกยอขนาด 600 มิลลิกรัม เป็นเวลา 6 ชั่วโมง มีผู้ป่วยที่มีอาการคลื่นไส้คิดเป็นร้อยละ 48 ซึ่งมีความแตกต่างอย่างมีนัยสำคัญกับกลุ่มคนป่วยที่ได้รับยาหลอก ซึ่งคิดเป็น ร้อยละ 80 ( $p\text{-value} = 0.04$ ) ส่วนการเกิดภาวะอาการคลื่นไส้และอาเจียน ของผู้ป่วยภายหลังการให้สารสกัดลูกยอในช่วงเวลาอื่น ๆ พบว่าไม่มีความแตกต่างทางสถิติเมื่อเทียบกับกลุ่มควบคุมที่ให้ยาหลอก นอกจากนี้ยังพบว่าไม่มีอาการข้างเคียงในผู้ป่วยทั้งสองกลุ่ม

**สรุป:** สารสกัดลูกยอที่ความเข้มข้น 600 มิลลิกรัม มีฤทธิ์และประสิทธิภาพในการรักษาและป้องกันการคลื่นไส้อาเจียนโดยเฉพาะในช่วง 6 ชั่วโมงแรกที่ผู้ป่วย ที่ได้รับสารสกัด และประสิทธิภาพดังกล่าว พบว่าเทียบเท่ากับการรักษา โดยใช้ scopolatin ขนาด 8.712 ไมโครกรัม

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