Prospective Study

# Horner Syndrome Following Intercostal Nerve Block Via an Anterolateral Approach in Breast Lumpectomy: A Prospective Nested Case-control Study

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**Background:** Lumpectomy is important for preventing malignant changes in benign tumors and diagnosing malignant tumors. Intercostal nerve blocks (ICNBs) are useful for breast lumpectomy as either the primary anesthetic or as an adjuvant anesthetic procedure. To our knowledge, no studies have evaluated the association between Horner syndrome and ICNB.

**Objectives:** This study aimed to explore the characteristics of and related risk factors for Horner syndrome after ICNB.

**Study Design:** A prospective, nested case-control study.

**Setting:** Fudan University Shanghai Cancer Centre from April 2020 through July 2020.

**Methods:** Patients scheduled for breast lumpectomy under ICNB from April 2020 through July 2020 in our hospital were recruited. The ICNB was introduced at the intersection of the midaxillary line and the inferior border of the ribs, according to the location of the mass. Horner syndrome indicators were assessed one, 5, 10, 15, 30, 45, and 60 minutes and 3, 6, 12 and 24 hours after ICNB. Personal data (age, body mass index [BMI], ASA classes), data on anesthetic (the puncture points, dose of local anesthetics, duration of ICNB, Horner syndrome indicators, other complications) and data on postoperative recovery (postoperative activity time, postoperative feeding time) were recorded. Univariate and multivariate logistic regression was used to estimate adjusted odds ratios and 95% confidence intervals.

**Results:** Ipsilateral Horner syndrome was found in 35 of 998 (3.5%) patients. Ipsilateral miosis, the first symptom to appear and last to disappear, occurred within 4 minutes and lasted 45 minutes to 240 minutes after ICNB. Seven patients showed obvious ipsilateral facial flushing. Logistic multivariate regression analysis showed that independent risk factors for Horner syndrome after ICNB were age ≤ 45 years, body mass index ≤ 18.5 $kg/m^2$, and the need for a second ICNB.

**Limitations:** Firstly, the patients in this study are all adult women, and the applicability of other populations is uncertain. Secondly, the flow trajectory of local anesthetics was not confirmed by imaging tracers.

**Conclusions:** ICNB via an anterolateral approach promoted enhanced recovery after breast lumpectomy. The incidence of Horner syndrome following ICNB for breast lumpectomy was 3.5%. Horner syndrome occurred on the ipsilateral side of the ICNB and was reversible. Younger age, lower BMI, and the need for a second ICNB were risk factors for Horner syndrome after ICNB.

**Key words:** Horner's syndrome, intercostal nerve block, breast lumpectomy, enhanced recovery

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Ptosis, miosis, anhidrosis, conjunctival hyperemia and enophthalmos are characteristic of the well-known Horner syndrome. Miosis was first described by Francois Pourfour du Petit in 1727 when considering results from an animal experiment involving resection of the intercostal nerves (1). The condition was formally described and later named after the Swiss ophthalmologist Johann Friedrich Horner in 1869 (2). Surgical procedures, such as pleurectomy (3), thoracoscopic sympathectomy (4-5), coronary artery bypass surgery (6) and internal jugular venous cannulation (7) were reported to cause the syndrome. Horner syndrome is mostly observed following anesthesia in pregnant women receiving lumbar epidural anesthesia and analgesia during labor (8-10) or cesarean delivery (11-14). This condition was also reported following thoracic epidural anesthesia for mastectomy (15), pediatric thoracic epidural anesthesia (16), superficial cervical plexus block (17), and brachial plexus block (18-21).

The incidence of Horner syndrome has been reported to be 0% to 4% after thoracoscopic sympathectomy (4, 22-24), 7.7% after coronary artery bypass surgery (6), 1.4% during thoracic epidural anesthesia (15), 2.6% during pediatric thoracic epidural anesthesia (16), 1.33% during lumbar epidural analgesia during labor (10), and 4% during lumbar epidural anesthesia for elective caesarean section (14). However, in a case series examined in 2010, only 6 (0.13%) out of 4,598 parturient women acquired Horner syndrome following epidural anesthesia (10). Horner syndrome related to anesthesia is generally not severe and persistent, but it can cause considerable patient discomfort and anxiety.

Compared with epidural analgesia, intercostal nerve blocks (ICNBs) have similar analgesic effects, with fewer complications and better postoperative recovery after thoracic surgery (25). ICNBs are widely used in clinical practice, such as breast surgery (26) and thoracoscopic surgery (27-32). It is especially beneficial for patients with cardiopulmonary diseases (33-34). In addition, ICNB can also be used to treat pain caused by thoracic herpes zoster (35) and traumatic rib fracture (36).

In 2020, breast cancer was estimated to be the most common cancer in women (37). Lumpectomy is especially important in preventing malignant changes in benign tumors and in diagnosing malignant tumors. Intercostal nerve blocks (ICNBs) are simple to perform and useful for breast lumpectomy as either the primary intervention or an adjunct procedure. In our hospital, there are nearly 5,000 breast lumpectomies performed with ICNBs every year. Horner syndrome was found to occur in some patients after ICNBs, causing panic and requiring identification of possible stroke events. To the best of our knowledge, no studies have evaluated the association between Horner's syndrome and ICNBs. We performed this prospective nested case-control study to prospectively explore the occurrence of Horner syndrome after ICNB for breast lumpectomy and related risk factors.

## Methods

Ethical approval for this study was provided by the ethics committee of Fudan University Shanghai Cancer Canter, Shanghai, China on April 15, 2020 (Number 2003215-9, Chairperson Prof. Chen Zhen) and registered at the Chinese Clinical Trial Registry (ChiCTR) (No. ChiCTR2000032296) on April 25, 2020. The patient enrollment date was April 30, 2020, and written informed consent was obtained from all patients.

Women scheduled for breast lumpectomy under ICNB and classified as American Society of Anesthesiologists (ASA) physical status I-III were eligible for the study. We excluded patients who received bilateral ICNBs and had a history of allergies to local anesthetics; infection at puncture sites; neuropathy, such as idiopathic facial paralysis; a history of stroke, transient ischemic attack; coagulopathy; anticoagulation or eye surgery; and ocular diseases, including glaucoma and cataracts. The patients were recruited the day before surgery and informed consent was obtained.

The patients did not receive any premedication. Standard monitoring was used throughout the intercostal nerve block and operation. An anterolateral approach was used for ICNBs in this study. The patients lay supine with the palms of the operative side under the head during ICNB administration to help expose the ribs. ICNB was performed using a 22-G needle (0.7 mm*32 mm for thin subcutaneous fat or 0.7 mm*80 mm for thick subcutaneous fat, Kindly Group, China) for local anesthetic injection and sterile techniques to avoid infection. The landmarks of the T3-T8 intercostal spaces were the inferior border of the ribs and the midaxillary line. The inferior border of the second rib and approximately 2.5 cm lateral to the midclavicular line were good landmarks to determine the T2 intercostal space (Fig. 1). To provide coverage for breast lumpectomy, we marked 3 to 6 intercostal spaces (from T2-T8 intercostal ribs) according to the location of the mass. Before ICNB, one mL of 1% lidocaine (100 mg/5 mL, Shangdong Hualu Pharmaceutical Co. Ltd, China) was given at each injection point for local skin anesthesia, and then ropivacaine (Naropin, 75 mg/10 mL, AstraZeneca, Cambridge, UK; 4 mL, 0.375%) was injected per intercostal space after confirmation that there were no blood or air bubbles via aspiration.

Following the injection, each patient was observed for 5 minutes to exclude pneumothorax or intravascular injection. Three anesthesiologists with more than 5 years of experience each performed the ICNBs under the direct supervision of one anesthesiologist with more than 25 years of experience. The effect of the ICNBs was confirmed by lightly touching the skin of the surgical site with a needle tip. Successful completion of an ICNB would result in skin numbness at the corresponding intercostal levels that had been blocked. If the effect of the ICNB was not satisfactory, another 4 mL of 0.375% ropivacaine was added to the relevant intercostal space. If the total amount of anesthetic drugs reached 40 mL and the anesthetic effect was still not satisfactory, general anesthesia was performed.

An independent anesthesiologist assessed the patients for signs of Horner syndrome and other complications one, 5, 10, 15, 30, 45, and 60 minutes and 3, 6, 12 and 24 hours after ICNB. Follow-up was carried out every 30 minutes until Horner syndrome disappeared completely. All intercostal space injections required for ICNB were completed, and the time of completion was considered time point 0. Horner syndrome was diagnosed by the occurrence of ptosis, miosis, or hyperemia (compared with the preoperative state and the contralateral side), with or without anhidrosis. When Horner syndrome was suspected, a second anesthesiologist confirmed the diagnosis, and the onset time and duration were recorded. Demographic data, such as age, body mass index (BMI, [kg/$m^2$] ), the total doses of local anesthetics, the duration of ICNB and the operation time and preoperative and postoperative pulse oxygen saturation ($FiO_2$ 21%) were recorded. The patients did not receive any other perioperative medication. Patients were divided into 2 groups (group with Horner syndrome and group without Horner syndrome); age was categorized as age ≤ 45 years and age > 45 years, BMI was categorized as BMI ≤ 18.5,18.5-25 and ≥ 25.

## Statistical Analysis

Continuous variables are shown as the mean and standard deviation (SD). Univariate analysis was first performed to identify potential predictor variables. Variables with a $P$ value < 0.2 according to univariate analysis and those considered to be clinically relevant were included in the multivariate analysis to identify independent predictors of the primary outcome. Logistic multivariate regression analysis (binary logistic analysis) was used to estimate the adjusted odds ratios and their 95% confidence intervals. The significance of the overall model was evaluated by omnibus tests of model coefficients. The goodness-of-fit of the overall model was evaluated by the Hosmer–Lemeshow goodness-of-fit statistic. The variance inflation factor was used to confirm that there were serious problems with multicollinearity. The magnitude of the association between risk factors and the occurrence of Horner syndrome after ICNB was summarized as the odds ratio with 95% confidence interval (CI), and $P$ values < 0.05 were considered significant. All statistical analyses were performed using the SPSS 23.0 software package (IBM Corp, Armonk, NY).

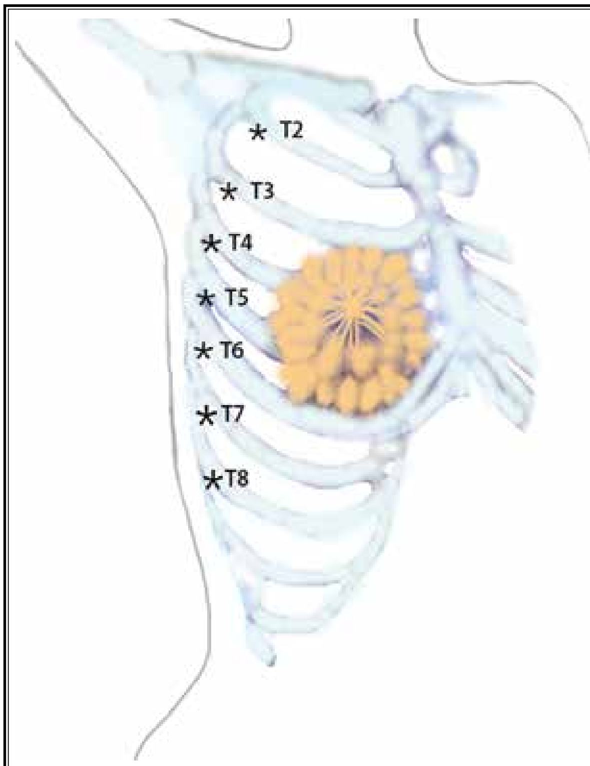



Fig. 1. *A model of the landmarks for intercostal nerve block. The crosses represent the sites of the T2-8 ICNB in this study.*

It was reported that the incidence of Horner syndrome was 4% during lumbar epidural anesthesia for elective cesarean section (14). Our pilot study showed that the incidence of Horner syndrome after ICNB was 4%. Based on a precision of 2% (38) and a dropout rate of 10%, we calculated that at least 469 patients would be required. To further explore the relevant risk factors for Horner syndrome, we expanded the sample size. Based on the concept of events per variable (EPV), 10 is an acceptable EPV for logistic regression (39). In this study, we set the number of possible risk factors at 4 according to the pilot study. Thus, the number of events was 40 due to the concept of EPV. The total sample size was 40/4% = 1,000 cases. Assuming a dropout rate of 10%, a total of 1,111 patients had to be included in the study.

## Results

There were 1,111 eligible patients from April 30, 2020 through July 20, 2020, scheduled for breast lumpectomy (Fig. 2). Sixty-eight patients were excluded according to the exclusion criteria. Thirty-six of these patients did not consent to receive an ICNB and were excluded from further study. Therefore, 1,007 patients were enrolled in the study. Nine patients were lost to follow-up. Finally, 998 patients completed the study; all patients were women. No patient required conversion to general anesthesia after ICNB.

Total follow-up time was 24 hours. Demographic data and ICNB-related characteristics in the study are shown in Table 1. Thirty-five of 998 patients developed Horner syndrome, for an incidence of 3.5% (95% CI, 2.4% to 4.7%). Among the 35 patients, all signs of Horner syndrome occurred on the same side as the ICNB. All 35 patients had ipsilateral miosis (Fig. 3), which occurred within 4 minutes and lasted 45 to 240 minutes after ICNB. Ipsilateral miosis was the first symptom to appear and the last to disappear; other symptoms developed almost simultaneously. Ipsilateral ptosis appeared almost simultaneously with miosis and was gradually aggravated, lasting for approximately 30 to 240 minutes.

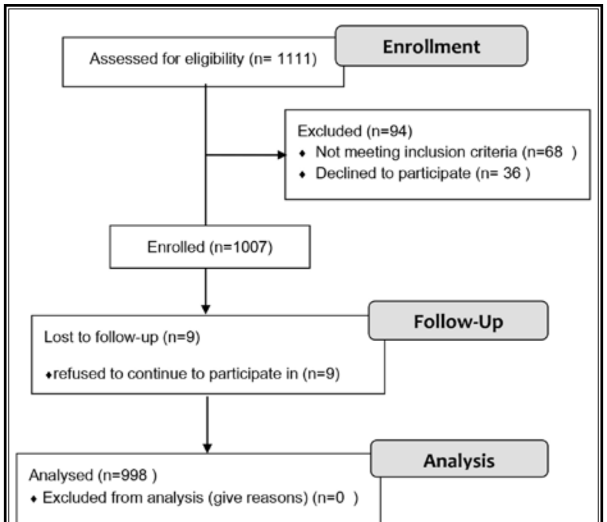



Fig. 2. *Flow diagram.*

Twenty-one patients presented with typical symptoms of Horner syndrome, including ipsilateral miosis, ptosis, conjunctival congestion, and enophthalmos, and complained of ipsilateral upper eyelid heaviness. One patient did not present with conjunctival congestion but did have the other 3 symptoms. One patient presented with only ipsilateral miosis and conjunctival congestion. Twelve patients had ipsilateral miosis only. One patient's ipsilateral miosis was observed only by the anesthesiologist and could not be documented with photos, which is probably due to her single eyelid and blepharoptosis. Among the patients with Horner syndrome, 7 showed obvious facial flushing on the same side as the ICNB, 3 complained of dizziness, one complained of ipsilateral gum swelling and pain, and one had ipsilateral arm numbness (Table 2).

In addition to Horner syndrome, 15 out of 998 patients complained of dizziness, 7 had ipsilateral arm numbness, 5 presented with a slight tremor, and 4 complained of numbness of the ipsilateral face and angulus oris without miosis and ptosis after ICNB. Two patients developed nausea and a decreased heart rate and recovered spontaneously after coughing. All the above symptoms disappeared within 10 to 15 minutes. No patient had pneumothorax.

There was no significant difference in the dose of ropivacaine or the postoperative analgesia time (VAS < 2) (Table 1). Furthermore, there was no difference between patients with Horner syndrome and patients without Horner syndrome in terms of the duration of the surgery or sleep quality on the first night after surgery (Table 1). Patients could be out of bed at any time after surgery, and there was no requirement for fasting after surgery (Table 1). The age of patients with Horner syndrome was younger than that of patients without Horner syndrome (34.34 ± 9.89 years vs 45.04 ± 10.86 years, $P < 0.01$) (Table 1). The BMI of patients with Horner syndrome was lower than that of patients without Horner syndrome (19.89 ± 2.75 vs 22.51 ± 3.19) (Table 1). Compared with patients without Horner syndrome, patients with Horner syndrome had a higher rate of second ICNB (37.14% vs 22.43%) (Table 1).

Univariate analyses indicated that the risk factors for Horner syndrome after ICNB were younger age (≤ 45 years), lower BMI (≤ 18.5), need for a second ICNB

Table 1. *Demographic data, ICNB-related characteristics in the study.*

| | Total | Group HS | Group without HS | *P* (Group HS VS Group without HS) |
|---|---|---|---|---|
| Age (yr), mean ± SD | 44.67 ± 11.01 | 34.34 ± 9.89 | 45.04 ± 10.86 | < 0.01 |
| BMI (kg/m$^2$), mean ± SD | 22.41 ± 3.20 | 19.89 ± 2.75 | 22.51 ± 3.19 | < 0.01 |
| Dose of ropivacaine (mg), mean ± SD | 85.18 ± 21.38 | 84 ± 15.52 | 85.25 ± 21.42 | > 0.05 |
| The uppermost costal nerve that is blocked, n(%) | | | | |
| $N_{T2}$/N (%) | 230/998 (23.05%) | 13/35 (37.14%) | 218/963 (22.63%) | < 0.05 |
| $N_{T3}$/(N- $N_{T2}$)% | 685/768 (89.19%) | 18/22 (81.82%) | 667/746 (89.41%) | > 0.05 |
| $N_{HS}$/ $N_{T2}$ Vs NHS / N- $N_{T2}$ | 13/230 (5.65%) Vs 22/768 (2.86%) | | | < 0.05 |
| Duration of the surgery (min) | 26.57 ± 8.07 | 25.11 ± 4.658 | 26.63 ± 8.163 | > 0.05 |
| Pos-pre $SpO_2$ changes,%, mean ± SD | 0.036 ± 0.236 | 0.040 ± 0.232 | 0.057 ± 0.232 | > 0.05 |
| Postoperative analgesia time (VAS < 2) | | | | |
| < 3 h | 25 (2.51%) | 0 | 25 | > 0.05 |
| 3-6 h | 353 (35.37%) | 12 (34.29%) | 352 (36.55%) | > 0.05 |
| 6-12 h | 498 (49.90%) | 20 (57.24%) | 478 (49.64%) | > 0.05 |
| 12-24 h | 72 (7.21%) | 3 (2.86%) | 69 (7.27%) | > 0.05 |
| no pain within 24 hours | 50 (5.01%) | 0 | 50 | > 0.05 |
| Sleep quality on the first night after surgery | | | | |
| good quality sleep | 835 (84.57%) | 31 | 813 (84.42%) | > 0.05 |
| poor sleep quality | 154 (15.43%) | 4 (11.43%) | 150 (15.78%) | |
| Postoperative activity time | Patients can get out of bed at any time after surgery | | | |
| Postoperative feeding time | No requirement of fasting after surgery | | | |

Abbreviations: T2, The second intercostal nerve; T3, The third intercostal nerve; N=number; VAS, visual analog scale. $N_{T2}$: Number of cases that received the second intercostal nerve block. $N_{T3}$: Number of cases in which the highest blocking nerve is the third intercostal nerve. $N_{HS}$: Number of cases of HS occurring. Pos-pre $SpO_2$ changes = postoperative $SpO_2$(FiO%=21%)- preoperative $SpO_2$ (FiO%=21%). HS=Horner syndrome.

and dose of ropivacaine (mg/kg) (Table 3). There was no multicollinearity among the 4 independent variables (all variance inflation factor < 3). A logistic multivariate regression analysis including these 4 variables showed that independent risk factors for Horner syndrome were age ≤ 45 years, BMI ≤ 18.5, and need for a second ICNB (Table 3). Omnibus tests of model coefficients showed that the model was statistically significant (*P*-value < 0.05); the Hosmer-Lemeshow goodness-of-fit test showed that the model had a high goodness-of-fit (*P*-value < 0.05).

## Discussion

In this study, the incidence of Horner syndrome during ICNB was 3.5%. Physical penetration of local anesthetics and the anatomical variation in the sympathetic nerve may be the mechanism of Horner syndrome after ICNB. Our hypothesis was supported by a cadaver study showing that dye injected around the intercostal nerve could penetrate the extrapleural space and reach the paravertebral space (40). ICNB has a risk of penetrating the sympathetic nerve chain and even affecting the central nervous system (40). In addition, anatomical variation in the sympathetic nerve may be one of the reasons for Horner syndrome after ICNB (41,42). Horner syndrome is caused by lesions or dysfunction in the "oculosympathetic pathway" running from the hypothalamus to the eye. The anatomical variation at levels C8-T4 may cause Horner syndrome (41,42). Then, we hypothesized that local anesthetics used in ICNB spread backward in the intercostal nerve sheath, first to the rami communicans and then to the sympathetic trunk and the sympathetic nerve fibers along the internal carotid artery, finally leading to Horner syndrome. In this study, the patients who received second ICNBs had an increased risk of Horner syndrome. As we hypothesized, the higher the level the ICNB was, the shorter the path of local anesthetic diffusion to the sympathetic trunk and the sympathetic fibers and the greater the probability of Horner syndrome.

Horner syndrome after epidural nerve block or ICNB may indicate a high sympathetic blockade; these patients should be monitored closely for autonomic complications. Along with Horner syndrome, trigemi-


Fig. 3. *Representative pictures of patients with Horner syndrome after ICNB. The pictures of patients No. 1 to 35, except for patients Nos. 5 and 15.*

Table 2. *Findings in patients with Horner syndrome.*

| Symptoms | Patient | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Breast operation side | L | L | L | L | L | L | L | L | L | L | L | L |
| Side of Horner syndrome | L | L | L | L | L | L | L | L | L | L | L | L |
| Age (yr) | 17 | 22 | 25 | 27 | 31 | 33 | 36 | 40 | 46 | 21 | 32 | 41 |
| BMI | 16.42 | 20.51 | 17.85 | 16.26 | 17.97 | 19.92 | 20.77 | 19.53 | 20.08 | 19.93 | 20.13 | 19.47 |
| Intercostal space of ICNB | T4-7 | T2-5 | T3-6 | T2-6 | T3-7 | T3-6 | T4-7 | T3-6 | T2-6 | T3-5 | T2-7 | T2-6 |
| Ropivacaine dosage (mg) | 75 | 90 | 90 | 105 | 105 | 75 | 75 | 60 | 75 | 60 | 105 | 75 |
| Pupil size (mm) (affected/normal) | 3.5/6 | 4.5/6.5 | 4/5.5 | 4/6 | 3/6 | 3/4.5 | 4/5 | 4/6 | 3/6 | 4.5/6 | 3.5/5 | 3/4.5 |
| Miosis onset time (min) | 1 | 4 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Duration of miosis (min) | 180 | 150 | 150 | 120 | 60 | 90 | 210 | 120 | 150 | 90 | 60 | 120 |
| Ptosis | + | + | + | + | + | + | + | + | + | + | + | + |
| Upper eyelid heaviness | + | + | + | + | + | + | + | + | + | + | + | + |
| Conjunctival congestion | + | + | + | + | + | + | + | + | + | + | + | + |
| Enophthalmos | + | + | + | + | + | + | + | + | + | + | + | + |
| Facial flushing | - | - | - | - | - | - | - | - | - | + | + | + |
| Dizziness | - | - | + | + | - | - | - | - | - | - | - | - |
| Arm numbness | - | - | - | - | - | - | - | - | - | - | - | - |
| Gum swelling and pain | - | - | - | + | - | - | - | - | - | - | - | - |

Table 2 (cont.). *Findings in patients with Horner syndrome.*

| Symptoms | Patient | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 |
| Breast operation side | L | R | R | R | R | R | R | R | R | R | L | R |
| Side of Horner syndrome | L | R | R | R | R | R | R | R | R | R | L | R |
| Age (yr) | 43 | 20 | 24 | 31 | 32 | 34 | 43 | 29 | 27 | 34 | 59 | 24 |
| BMI | 20.83 | 18.49 | 19.23 | 17.63 | 22.94 | 19.35 | 19.57 | 21.30 | 17.1 | 17.63 | 16.14 | 18.73 |
| Intercostal space of ICNB | T2-7 | T3-6 | T3-6 | T3-7 | T2-6 | T2-7 | T3-6 | T2-5 | T3-6 | T2-4 | T3-6 | T3-7 |
| Ropivacaine dosage (mg) | 90 | 75 | 90 | 75 | 75 | 90 | 90 | 105 | 90 | 60 | 90 | 90 |
| Pupil size (mm) (affected/normal) | 3.5/5.5 | 4/6.5 | 4/6 | 4.5/5.5 | 3.5/5 | 3/4.5 | 3.5/5.5 | 3/5 | 2/4 | 4/5.5 | 2.5/3.5 | 4.5/5.5 |
| Miosis onset time (min) | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1.5 | 1 | 1 |
| Duration of miosis (min) | 90 | 120 | 120 | 90 | 120 | 60 | 150 | 240 | 240 | 180 | 180 | 45 |
| Ptosis | + | + | + | + | + | + | + | + | + | + | - | - |
| Upper eyelid heaviness | + | + | + | + | + | + | + | + | + | + | - | - |
| Conjunctival congestion | + | + | + | + | + | + | + | + | + | - | + | - |
| Enophthalmos | + | + | + | + | + | + | + | + | + | + | - | - |
| Facial flushing | + | - | + | - | - | - | - | + | + | - | - | - |
| Dizziness | - | - | - | - | - | - | - | - | - | + | - | - |
| Arm numbness | - | - | - | - | - | - | - | - | - | + | - | - |
| Gum swelling and pain | - | - | - | - | - | - | - | - | - | - | - | - |

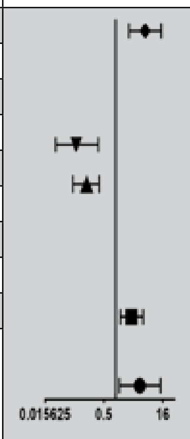
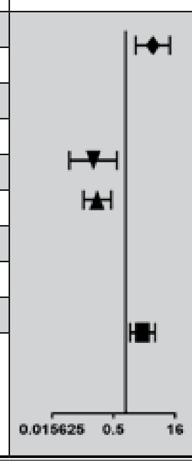
nal nerve palsy (43) and ipsilateral brachial plexus block (44) were also reported following epidural blockades. Patients with Horner syndrome may be complicated by drops in blood pressure (45) and nasal obstruction and dyspnea (26). In this study, very few patients presented with concurrent obvious ipsilateral facial flushing, gum swelling, and pain, or numbness of the ipsilateral face, angulus oris, and arm, which may be due to a sympathetic nerve block along the external carotid artery (Fig. 4), trigeminal nerve palsy, or brachial plexus block.

Table 2 (cont.). *Findings in patients with Horner syndrome.*

| Symptoms | Patient | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **25** | **26** | **27** | **28** | **29** | **30** | **31** | **32** | **33** | **34** | **35** |
| Breast operation side | R | L | L | L | L | L | R | L | R | R | R |
| Side of Horner syndrome | R | L | L | L | L | L | R | L | R | R | R |
| Age (yr) | 27 | 30 | 31 | 33 | 35 | 40 | 40 | 43 | 49 | 49 | 54 |
| BMI | 20.83 | 18.43 | 29.14 | 17.2 | 19.60 | 19.72 | 25.04 | 22.10 | 18.73 | 21.45 | 26.62 |
| Intercostal space of ICNB | T2-6 | T4-7 | T3-6 | T3-6 | T2-5 | T3-6 | T3-6 | T3-6 | T2-5 | T4-8 | T3-8 |
| Ropivacaine dosage (mg) | 90 | 75 | 75 | 60 | 105 | 60 | 75 | 90 | 105 | 75 | 120 |
| Pupil size (mm) (affected/normal) | 4/5.5 | 3.6/6 | 3/4 | 3.5/5 | 2.5/4 | 4/5 | 2.5/3.5 | 3.5/5.5 | 3.5/5 | 4/5.5 | 3/4 |
| Miosis onset time (min) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Duration of miosis (min) | 90 | 120 | 90 | 60 | 45 | 90 | 45 | 60 | 45 | 240 | 90 |
| Ptosis | - | - | - | - | - | - | - | - | - | - | - |
| Upper eyelid heaviness | - | - | - | - | - | - | - | - | - | - | - |
| Conjunctival congestion | - | - | - | - | - | - | - | - | - | - | - |
| Enophthalmos | - | - | - | - | - | - | - | - | - | - | - |
| Facial flushing | - | - | - | - | - | - | - | - | - | - | - |
| Dizziness | - | - | - | - | - | - | - | - | - | - | - |
| Arm numbness | - | - | - | - | - | - | - | - | - | - | - |
| Gum swelling and pain | - | - | - | - | - | - | - | - | - | - | - |

Abbreviations: BMI, Body Mass Index; ICNB, intercostal nerve block.

Table 3. *Risk factors for Horner syndrome.*

| | | Univariate analyses | | | Multivariate analyses | | |
|---|---|---|---|---|---|---|---|
| | **n/N, %** | | **OR (95%CI)** | ***P*-value** | | **OR (95%CI)** | ***P*-value** |
| Age (yr) | | | | | | | |
| ≤45 | 30/531(5.65%) | | | | | | |
| >45 | 5/467(1.07%) |  | 5.53(2.13-14.38) | <0.01 |  | 4.77(1.807-12.576) | <0.01 |
| BMI (kg/m²) | | | | | | | |
| ≤18.5 | 11/77(14.29%) | | | | | | |
| 18.5-25 | 21/737(2.85%) | | 0.10(0.03-0.37) | <0.01 | | 0.155(0.04-0.59) | <0.01 |
| ≥25 | 3/184(1.63) | | 0.18(0.08-0.38) | <0.01 | | 0.19(0.09-0.43) | <0.01 |
| The second intercostal space | | | | | | | |
| Y | 14/230(6.09%) | | | | | | |
| N | 21/768(2.73%) | | 2.59(1.31-5.15) | <0.01 | | 2.659(1.308-5.403) | <0.01 |
| Dose of ropivacaine (mg/kg) | | | | | | | |
| | 35/998 | | 4.01(1.18-13.66) | 0.023 | | - | 0.353 |





The results of the univariate and multivariate analyses were visualized in forest plots. Abbreviations : BMI, body mass index; OR, odds ratio; CI: confidence interval. n=number of patients with Horner syndrome.

As the anesthetic effect decreases, these symptoms can resolve spontaneously. The symptoms of dizziness and slight tremor may be the result of postural changes by the patients and a low room temperature. Therefore, performing ICNB while the patient is awake can alert providers to unexpected complications.

The obese women had relatively more fat on the rib cage than the lean women (46). Therefore, for patients with a low BMI, local anesthetics might spread more widely since they are not easily absorbed by the surrounding adipose tissue. Generally, elderly patients are more susceptible to local anesthetics. However, in this study, younger patients were more susceptible to Horner syndrome. Our results showed that "reverse transport" of local anesthetics (shown in Fig. 4) may be more prevalent in younger patients. The types and dosages of local anesthetics seemed to be unrelated to the occurrence of Horner syndrome. This condition was reported to occur whether the patients received bupivacaine (9), levobupivacaine (16), or ropivacaine (15,18). Multivariate analysis showed no significant difference in the ropivacaine dose between patients with and without Horner syndrome in this study.

The onset time of Horner syndrome following 6 mL of 0.25% bupivacaine for lumbar epidural analgesia for labor (9) and a bolus of 0.375% or 0.5% ropivacaine (15 mL) for thoracic epidural anesthesia (15) was reported to be 20 minutes and 30 minutes, respectively, and it resolved gradually and spontaneously over the following 30 to 180 minutes. In this study, Horner syndrome occurred rapidly, within 4 minutes after ICNB, and lasted for 45 to 240 minutes. Ipsilateral miosis was the first symptom to appear and the last to disappear, indicating that the sympathetic nerve innervating the sphincter pupillae, dilator pupillae, and the ciliary muscle was more susceptible to local anesthetics than that innervating the levator palpebrae superioris. Horner syndrome may also result in anhidrosis, but this symptom is difficult to assess in the operating room due to the constant temperature. Most cases of Horner syndrome after anesthesia are reversable.

Horner syndrome after epidural anesthesia is often unilateral, which may be caused by the influence of the patient's position and the membranous structure between the dura mater and periosteum on the diffusion of local anesthetics, as well as the difference in the original segments of the spinal cord that innervate the sympathetic nerves of the eyes in the patient. In this study, Horner syndrome occurred only on the ipsilateral side of the ICNB, indicating that the majority of local anesthetics were injected away from the nerve roots, and there was little chance for local anesthetics to infiltrate into the prevertebral spaces.

There were several limitations to this study: firstly, the effect of other single ICNBs on the incidence of Horner syndrome could not be effectively analyzed because at least 3 intercostal nerves were anesthetized for each operation. Secondly, all patients were women. Therefore, caution should be considered in extending the results to men. Thirdly, the flow trajectory of local anesthetics was not confirmed by imaging tracers. Finally, ultrasound was not used in this study. Ultrasound is very useful to avoid pneumothorax during ICNB. However, the success rate of ICNB was similar with and without the use of ultrasound in our hospital. Whether the incidence of Horner syndrome after ICNB decreases with the use of ultrasound needs further study.

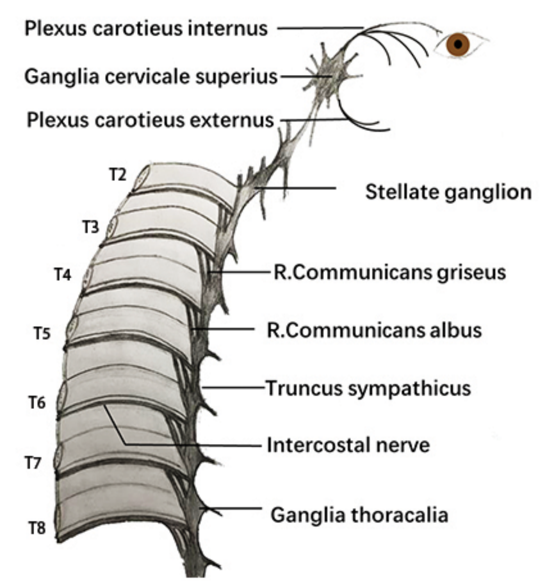



Fig. 4. *Schematic diagram of the mechanism hypothesis. We hypothesized that local anesthetics spread backward in the intercostal nerve sheath, first to the rami communicans and then to the sympathetic trunk and the sympathetic nerve fibers along the internal carotid artery to cause Horner syndrome or along the external carotid artery to cause obvious ipsilateral facial flushing.*

ICNB has been proven to be an important link in accelerating recovery after breast surgery, reducing the use of opioids (35). In this study, postoperative activities and eating time were not affected by anesthesia. Also, the sleep efficiency of the first night after surgery was 84.57%, which was much higher than that of the first night after general anesthesia (47). It can be inferred that ICNB alone is beneficial to patients with sleep apnea (33). At present, there are few studies on ICNB alone for benign breast tumour resection and malignant tumour diagnosis, only in the form of case reports (48,49) and most of the studies are on general anesthesia combined with ICNB (26) or other combined anesthesia techniques (50). General anesthesia can mask Horner syndrome, and Horner syndrome after ICNB combined with general anesthesia needs to be differentiated from other complications (such as stroke events) to avoid unnecessary measures. This article can provide a basis for a differential diagnosis.

## Conclusions

In summary, ICNB via an anterolateral approach promoted enhanced recovery after breast lumpectomy. Younger age, lower BMI, and the need for a second ICNB were risk factors for Horner syndrome.

### Availability of Data and Materials

https://pan.baidu.com/s/1tz2ticyBCDMZ3Pytt8l0_Q, password: a591.

### Author Contributions

Study design: WTH, XJY, MLW.
Patient recruitment: WTH, XJY, MLW. LC
Data and preliminary analyses: WTH, JZ, XJY.
Final data analysis: WTH, MZL, JZ.
Writing paper: WTH, JZ.
Revising paper: WTH, JZ, CN, CHM.

### Ethics Approval and Consent to Participate

Ethical approval for this study was provided by the ethics committee of Fudan University Shanghai Cancer Canter, Shanghai, China on April 15, 2020 (Number 2003215-9, Chairperson Prof. Chen Zhen) and registered at the Chinese Clinical Trial Registry (ChiCTR) (No. ChiCTR2000032296). The study was prospectively registered on April 25, 2020. URL: http://www.chictr.org.cn. The first patient in the study was enrolled on April 30, 2020. Written informed consent and consent to publish were obtained from all patients.

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