Evaluation of Clinical Efficacy of Intravenous Glyco-P® (Glycopyrrolate)

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ABSTRACT

Background: Glycopyrrolate has been widely used globally as an adjunct in anesthesia since early 1970's. However, this agent has never been used in Thailand until recent introduction of the Glyco-P® (0.2 mg IV glycopyrrolate). The clinical efficacy and safety of intravenous glycopyrrolate in Thai population was unknown.

Objective: To evaluate the clinical efficacy of intravenous glycopyrrolate in 3 areas 1) antisialagogue 2) effect on heart rate and 3) anticholinergic effects when used with neostigmine for neuromuscular blockade reversal.

Methods: Single-centered, prospective observational study, which enrolled 121 ASA 1-3 patients receiving intravenous sedation or general anesthesia. The patients were given an IV glycopyrrolate and had their data collected and categorized by clinical indications into 3 groups-secretion group (SCR), heart rate group (HR) and reversal of neuromuscular blockade group (NMR). We recorded heart rate and blood pressure at baseline and every 5 minutes and recorded secretion score every 10 minutes after treatment.

Results: Intravenous glycopyrrolate demonstrated good antisialagogue properties as 76.1-85.6% of patients in SCR group recorded minimal secretion score, between 0-1 out of 5, at 10-20 minutes. A mild to modest chronotropism was observed as mean heart rate was increased from 72.85 to 79.85 within 5 minutes. When used with neostigmine for reversal of neuromuscular blockade, the well-balanced anticholinergic effect was seen as stable heart rate and minimal secretion.

Conclusion: An intravenous Glyco-P® demonstrates its clinical efficacy in Thais at the same recommended dose as previously described in western population for both antisialagogue and stable heart rate when used alone and used in conjunction with neostigmine for neuromuscular blockade reversal.

Keywords: Glycopyrrolate; Glyco-P®; antisialagogue; secretion reduction; anticholinergic; atropine (Siriraj Med J 2017;69:24-31)

INTRODUCTION

Glycopyrrolate is a synthetic anticholinergic drug available as an intravenous form. It is in the same class as atropine and scopolamine (hyoscine), but exerts different characteristics. Atropine possesses strong chronotropism, weak antisialagogue, fast onset and short duration. Glycopyrrolate has mild to moderate chronotropism, moderate to strong antisialagogue, fairly quick onset (3-5 minutes) with intermediate duration (30-60 minutes). Scopolamine (hyoscine) also has strong antisialagogue, but its use is limited to endoscopy suite. It can readily pass blood brain barrier and cause sedation, particularly in elderly patients. The usual dosage is 4 mcg/kg for saliva reduction which should be given 15-30 minutes preoperatively, it is also given at the ratio of 0.2 mg per 1 mg of neostigmine (1:5) for neuromuscular blockade reversal.[1,2]

In Thailand, atropine has long been used as an intravenous anticholinergic in anesthesia service. Its antisialagogue effect is trivial. It usually causes early onset of marked tachycardia with subsequent bradycardia when used with neostigmine for neuromuscular blockade reversal secondary to duration mismatch between the 2 drugs. There are several reports of dysrhythmias i.e.

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atrial fibrillation, ventricular fibrillation or cardiac arrest associated with uses of this combination.[3-6]

Intravenous glycopyrrolate has never been used in Thailand. The standard recommended dosage is based on studies in western population dated back in 1970s when the medication was initially introduced.[7-9] Most locally trained Thai physicians are not familiar with the dosage and its safety margin. The institutional pharmacy also encouraged us to evaluate its effectiveness.

Patients under anesthesia or sedation often require airway management. Excessive oropharyngeal and tracheal secretion are undesirable and it may lead to airway related complications i.e. broncho-laryngospasm, aspiration, secretion obstruction, and etcetera. During airway instrumentations, salivation is induced which may impede and obscure the airway view. Prevention of secretion is usually indicated in patients with difficult airway and in patients who are to be turned into lateral or prone position. Lastly, the onset and duration of glycopyrrolate is similar to neostigmine (one of the intravenous cholinergic agents used for reversal of neuromuscular blockade).[10-12] In this study, we tested the efficacy of intravenous Glyco-P® for secretion reduction and effect on heart rate (HR) when used alone and also when used with neostigmine. (ClinicalTrial.gov ID: NCT02102542)

MATERIALS AND METHODS

The research protocol was reviewed and approved by institutional ethic committee. Written informed consent was obtained from all patients or their legal surrogates. We enrolled patients, over 18 years, ASA 1-3, who underwent anesthesia or sedation during July 2012 to April 2013. Inclusion criteria were patients with suspected or proven difficult airway, patients in prone or lateral position, patients scheduled for airway related procedures, patients with severe bradycardia (HR ≤ 50 without symptoms or HR ≤ 60 with symptoms or hypotension) and patients who need a reversal following neuromuscular blockade. We excluded pregnant and breast feeding women, patients with Sjögren's syndrome, glaucoma, myasthenia gravis and patients with baseline HR > 120 bpm.

Intravenous glycopyrrolate (glycopyrronium bromide) used in this study was Glyco-P® (Kwendelwal laboratories, India) which was introduced in Thailand by Masu CO., Ltd. The medication is supplied as an ampule of 0.2 mg of glycopyrrolate in 1 mL diluent. The medication was tested in vitro and was approved by Thai food and drug administration [1C 101/25539(NC)].[13]

Patients who met the aforementioned inclusion criteria and consented for this research could receive the medication either preoperatively (prevention of salivation), intraoperatively (treatment of hypersalivation or bradycardia) or postoperatively (for reversal when muscle relaxant was used). The HR, blood pressure (BP) at the time before medication administration was recorded as baseline values by one of the research teams. The monitoring system used was either Philips MP30, MP50 (software rev 6.45), MP70 (software rev. G.01.80), SureSigns VS3 (software rev. 04.62) (Philips, Andover, MA, USA) or Nihon or Maquet. The patient's oropharyngeal secretion and or tracheal secretion (if intubated) score at baseline was also assessed by the anesthesia personnel who was not part of the research team and was blinded to the treatment. For preoperative and intraoperative uses, 0.2 mg or 4 mcg/kg of glycopyrrolate was administered. The HR and BP were recorded every 5 minutes for 20 minutes; secretion scores were assessed again at 15 and 20 minutes by the same person. If the first dose did not work (no drying effect for secretion or no increase in HR for bradycardia), the second dose was administered and the BP and HR were recorded as they were with the first dose.

For postoperative use (for reversal of neuromuscular blockade) – the glycopyrrolate at the ratio of 0.2 mg per 1 mg of neostigmine) was administered sequentially in a separate syringe (glycopyrrolate first, immediately followed by neostigmine). The HR, BP and secretion score before treatment was recorded as baseline values. The HR and BP were recorded every 5 minutes and secretion score was assessed again every 10 minutes until 30 minutes.

A patient might receive monitored anesthesia care, IV sedation, regional anesthesia or general anesthesia. We did not provide restriction to medications or techniques used in either modality of anesthesia service. The research team might also be part of the primary anesthesia team.

One patient may receive medication at either period if they met the indications. This possibly allows more than one data set per patient to be recorded and used for analysis. We categorized the data set based on treatment effects into 3 categories which are 1) Secretion effect (SCR), 2) HR effect (HR) and 3) When used with neostigmine for neuromuscular blockade reversal (NMR).

Statistical analysis

Clinical effectiveness of glycopyrrolate at appropriate dose in western population is estimated at 80 ± 10%.[11-12] The sample size was calculated based on an assumption of 95% confidence interval, and 2 sided type I error = 0.05). For each treatment effect dataset, there should be at least 65 data set in each group. All collected data were

analyzed with IBM® SPSS® Statistics (for MAC, version 20). For antisialagogue efficacy, comparisons of secretion score were analyzed by Friedman test. Each pair of secretion scores at different times was analyzed by Wilcoxon Signed-Rank test. For effect on HR, the comparisons of HR between baseline and other time intervals were analyzed with multivariate test. The p-value that was ≤ 0.05 was considered to be statistically significany.

RESULTS

A total of 121 patients were enrolled, and 65 patients were treated preoperatively or intraoperatively for secretion. All of these 65 patients had their HR recorded before and after medication and their HR dataset could be used for both SCR and HR data set groups. There were 17 patients in this group who also needed neuromuscular blockade reversal and received glycopyrrolate which yielded the third data set for NMR. Another 6 patients received medications for bradycardia and did not have their secretion score completely assessed, so these 6 patients could only be included in HR data set group. Another 50 patients received the glycopyrrolate just for neuromuscular blockade reversal and so they were only included in NMR data set group. Since one patient may yield a data set in either, both or all of three treatment effect groups (Fig 1), the initial data set in SCR, HR and NMR groups were 65, 71 and 67 patients accordingly. When final analysis was performed, there were 2 patients who received glycopyrrolate for secretion with incomplete data record. After exclusion, we were left with 63, 69 and 67 patients eligible for statistical analysis in SCR, HR and NMR groups, retrospectively. The demographic data, types of surgery or procedure and baseline characteristics of all patients are shown in Table 1.

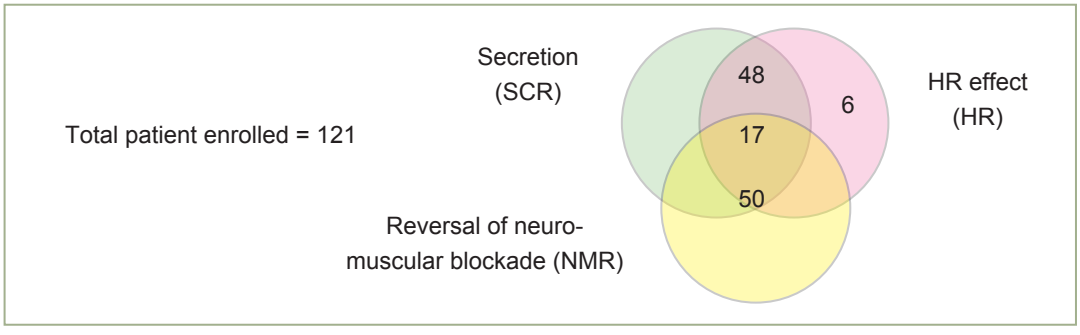

Fig 1. The subgroup of data set collected from patients based on their initial primary indication of treatment.

TABLE 1. Demographic data, type of procedures and baseline characteristics.

Variables	
Number of patients (after exclusion)	121
Age	
Median (yr)	55
Male (%)	40.2
Female (%)	59.8
Type of operation or procedures	
ENT	21
Eye	2
GI endoscopy	11
Gynecological surgery	24
Intra-abdominal surgery	15
Intra-thoracic surgery	23
Neurological surgery	13
Orthopedic surgery	3
Others	8
Vascular surgery	1

Most patients (51/63 or 81%) in SCR group received glycopyrrolate for prevention of secretion while 12 patients (19%) received glycopyrrolate as a treatment for hypersalivation or hypersecretion. Glycopyrrolate significantly lowers secretion score throughout the entire 20 minutes after IV administration (P = 0.001 when compared with secretion score at 0 vs. 10 min vs. 20 min by Friedman test). This significant reduction was also observed when compared between 0 vs. 10 minutes (p = 0.006) and 0 vs. 20 minutes (P = 0.001). There were no significant differences of secretion score between 10 minutes and 20 minutes (P = 0.059). Most patients received only 1 dose while 2 patients (2/63 = 3.2%) required a repeated dose for secretion reduction. Over all secretion scores at 0, 10 and 20 minutes is displayed in Table 2 and also as a stacked bar chart in Fig 2.

Those 2 excluded patients in SCR group also resulted in reduction of data sets in HR group from 71 to 69 patients. Most patients (63/69 or 91%) had their HR recorded while receiving glycopyrrolate for salivation reduction as a primary purpose. Only 6 patients (8.7%) received glycopyrrolate for bradycardia. The mean HR

TABLE 2. Secretion score at 0 min (baseline), 10 min and 20 min following IV glycopyrrolate.

Secretion score	Number of patients (N=63) -percentage is displayed in ( )		
	0 min (baseline)	10 min	20 min
0	4 (6.3)	10 (15.8)	13 (20.6)
1	43 (68.3)	38 (60.3)	41 (65.0)
2	4 (6.3)	13 (20.6)	7 (11.1)
3	4 (6.3)	2 (3.2)	2 (3.2)
4	6 (9.5)	0	0
5	2 (3.2)	0	0

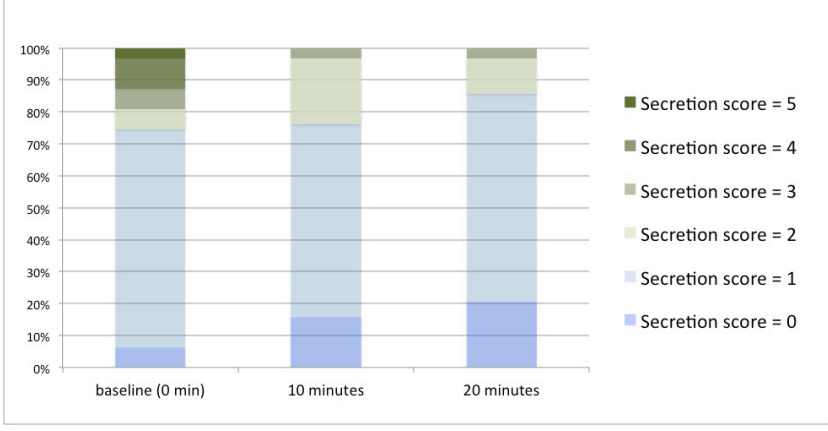

Fig 2. Stack bar chart of secretion scores of patients in SCR group at 0, 10 and 20 minutes.

(bpm) was slightly increased (72.85 vs. 79.85) when the baseline and at 5 minutes ($P < 0.001$) were compared. There were no significant differences of mean HR between 5 minutes, 10 minutes, 15 minutes and 20 minutes (Table 3).

There were 19 patients (27.5%) whose HR was unchanged, 25 patients (36.2%) with <10 bpm increase in HR and also 25 patients (36.2%) with >10 bpm increase in HR (Table 4).

TABLE 3. The mean heart rate (beat per minutes) of patients in heart rate group (N = 69).

HR (bpm)	Baseline	5 minutes	10 minutes	15 minutes	20 minutes
Mean	72.85	79.85	80.04	81.54	81.47
Median	73.00	75.00	80.00	82.00	80.00
SD	18.54	20.04	19.54	16.43	16.2
Minimum	37	43	41	48	43
Maximum	115	125	126	124	128

TABLE 4. The number of patients with increase in heart rate when received glycopyrrolate alone (N = 69).

	Frequency	Percent	Valid Percent	Cumulative percent
No change in HR	19	27.5	27.5	27.5
Increase HR less than 10 bpm	25	36.2	36.2	63.7
Increase HR between 10-20 bpm	13	18.8	18.8	82.5
Increase HR >20 bpm	12	17.4	17.4	100
Total	69	100	100	

In 6 patients who received glycopyrrolate for treatment of bradycardia, half of these (3/6) required the repeated dose or rescue medications (0.6 mg of atropine or 6 mg of ephedrine) to restore HR and or blood pressure to normal values.

In NMR group, most patients (58/67-86.6%) started with relatively dry secretion (score 0-2) at baseline. The drying effect was well noted at 30 minutes when 94% (63/67) of patients' secretion score were recorded at 0-1 (Table 5). The mean HR was slightly increased when compared between the baseline value (73.9 bpm) versus at 5 minutes (82.73), P-value <0.001 (Table 6). There were no significant changes in HR afterward. At 30 minutes, the mean HR was almost identical to the baseline value. There were no reports of dysrhythmias. The box plot graph of HR changes in NMR group is displayed in Fig 3.

TABLE 5. Secretion score at 0 min (baseline), 10 min, 20 min and 30 min following a combination of glycopyrrolate and neostigmine for neuromuscular blockade reversal.

Secretion score	Number of patients (%)			
	0 min (baseline)	10 min	20 min	30 min
0	3 (4.5)	6 (9.0)	12 (17.9)	24 (35.8)
1	41 (61.2)	34 (50.7)	47 (70.1)	39 (58.2)
2	14 (20.9)	19 (28.4)	7 (10.4)	3 (4.5)
3	6 (9.0)	6 (9.0)	1 (1.5)	1 (1.5)
4	1 (1.5)	2 (3.0)	-	-
5	2 (3.0)	-	-	-

TABLE 6. Mean heart rate of patients in NMR group (N=67) at baseline and each 5-minute interval up to 30 minutes.

	Mean heart rate (bpm)	Standard deviation
Baseline	73.9	15.34
5 minutes	82.73	15.28
10 minutes	79.88	15.82
15 minutes	78.28	15.14
20 minutes	77.10	15.81
25 minutes	75.30	15.95
30 minutes	73.76	16.01

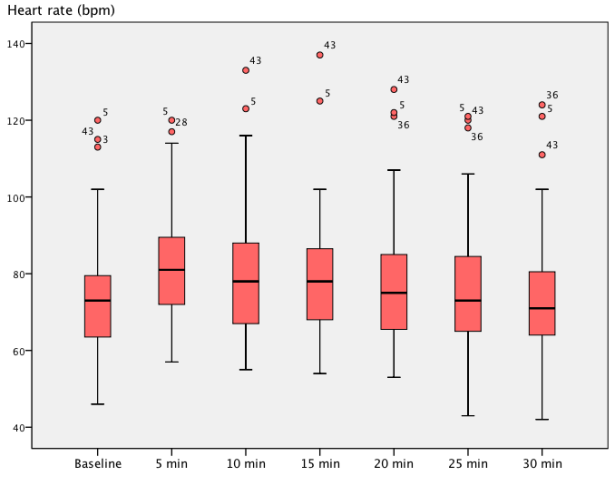

Fig 3. Box plot graph of heart rate of patients in NMR group at baseline and each 5-minute intervals up to 30 minutes following administration of glycopyrrolate and neostigmine (ratio of 1:5).

DISCUSSION

Glycopyrrolate or glycopyrronium bromide (pyrrolidinium 3-[cyclopentylhydroxy/phenylacetyle) oxy]1,1-dimethy bromide) was introduced in 1970s.[7-9] It has been used worldwide as an adjunct in anesthesia for secretion reduction and co-administration with neostigmine for muscle reversal.[20] Glycopyrrolate is classified as an orphan drug in Thailand, with a small market share leading to a lack of interest for import or manufacturing. Its recent introduction was met with poor adoption rate due to lack of familiarity and confidence in using this imported medication (Glyco-P®). We designed this research to confirm its clinical efficacy and prove that recommended dosage used in western population is applicable to Thai patients.

Glyco-P® was tested in-vitro by an independent laboratory as a process for Thai-FDA registration. However, it has never been tested clinically. The primary research question was whether Glyco-P® would actually work and the secondary question was to test that the recommended dose was appropriate for Thais.

Our first limitation was the study design. The ideal study should be a randomized controlled trial comparing between Glyco-P® and the other western brands of glycopyrrolate i.e. Robinul® (widely used in the U.S.).[11] Unfortunately, we do not have Robinul® or other brands of this medication. The other scenario was to compare Glyco-P® with atropine or placebo. However, the differences in anticholinergic properties as mentioned earlier makes this design irrelevant to the research questions. An observational prospective study was then designed to validate the clinical efficacy of Glyco-P®.

Another limitation was the derivation of different groups of data sets from the same patient. This design caused non-uniform distribution among each group (65, 69 and 67 patients in SCR, HR and NMR groups, respectively). After exclusions of 2 patients in SCR and HR groups, the final number of data sets in the SCR group was reduced to 63, which was slightly underpowered.

A single dose of 0.2 mg has shown its effectiveness in prevention of secretion and treatment of hypersecretion. The majority of patients who received the medications for prevention (51/63 -81%) were treated when their baseline secretion score was 0-2. A smaller number of patients (12/63- 19%) with baseline secretion score of 3-5 received the medication as a treatment. The result confirmed that when administering glycopyrrolate for prevention of secretion, the medication should be given at least 10-20 minutes before airway instrumentation with laryngoscope or special airway equipment.[21-22]

We found that glycopyrrolate increased the HR to a varying degree in the majority of the patients (72.5%), while 27.5% of patients showed no changes in HR. Although we had only 6 patients received glycopyrrolate for bradycardia, about half of this subgroup demonstrated a failure of treatment. This finding was consistent with the ACLS guideline that recommends atropine, not glycopyrrolate, as the first drug of choice for treatment of symptomatic bradycardia.[23]

Pharmacologically, glycopyrrolate has the onset and duration which matches better with neostigmine when compared with atropine for reversal of neuromuscular blockade.[10-12] The results from our study also confirmed this finding in Thais. Most patients demonstrated stable HR, devoid of excessive secretion for up to 30 minutes. The only cumbersome part was the recommended dose of 0.2 mg of glycopyrrolate per 1 mg of neostigmine (1:5).[12] Since the unit dose of neostigmine in Thailand is 2.5 mg, this means that 2.5 ampules of Glyco-P® was needed. Alternatively, clinicians can use 2 ampules of Glyco-P® (0.4 mg of glycopyrrolate) in conjunction with just 2 mg of neostigmine. Itthichaikulthol W, et al reported that 0.2 mg of glycopyrrolate combined with atropine 0.6 mg and neostigmine 2.5 mg demonstrated an initial increase in heart rate similar to that found in patients who received 1.2 mg of atropine and 2.5 mg of neostigmine.[24] Hence, if stable HR is of paramount importance (for example in elderly patients, patients with known ischemic heart disease), we strongly recommend the use of only glycopyrrolate (not combined glycopyrrolate and atropine) to be used in conjunction with neostigmine for neuromuscular blockade reversal. There are also some concerns for cost increment because Glyco-P® is billed at THB 37 in our institution while atropine is only THB 3.25. This concern is totally comprehensible since we never had atropine alternatives before, and all Thai patients have been given atropine and neostigmine combination. Truthfully, there are some unreported unfortunate minorities with serious consequences (i.e. acute myocardial infarction, dysrhythmias and etcetera) and they often do require further treatments, longer hospital stay or ICU stay which can cost far more than THB 37. Theoretically and evidently, glycopyrrolate has been demonstrated as a better anticholinergic drug to be used with neostigmine.[14-16] It has been a gold standard neostigmine match for decades in several western countries. To ease one's concern about cost, perhaps, case selection, i.e., elderly patients, patients with limited cardio-pulmonary reserve, patients with coronary artery disease, patients with difficult airway and etcetera, should be considered.

The authors speculate that when market share of glycopyrrolate has increased, the Thai GPO (Government Pharmaceutical Organization) may start manufacturing or other pharmaceutical companies may import the other brands of glycopyrrolate which may bring the cost down to similar price to atropine.

CONCLUSION

Intravenous Glyco-P®, which contains glycopyrrolate 0.2 mg/mL, has shown efficacy as an antisialagogue in Thais at the same recommended dose as in the western population. It has mild to moderate tachycardia effect, but cannot be reliably used for treatment of symptomatic bradycardia. Glycopyrrolate also provides stable heart rate and excellent drying effect when combined with neostigmine for neuromuscular blockade reversal for up to 30 minutes.

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Potential conflict of interest

All study medications (Glyco-P®) were supplied by Masu company.

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Appendix: Secretion score

Score	Description
0	Dry mucosa or dry mouth detected. Awake patients complain of dry mouth.
1	Slightest amount of saliva/secretion, no suctioning required and nothing yielded from suctioning.
2	Small amount of saliva/secretion. Suctioning yields saliva/secretion no more than 10 mL.
3	Medium amount of saliva/secretion. Suctioning yields saliva/secretion about 11-20 mL.
4	Large amount of saliva/secretion. Suctioning yields saliva/secretion 21-30 mL or required more than 1 suctioning.
5	Massive amount of saliva, drooling out of patient's mouth or ETT, require multiple suctions. Total amount of saliva/secretion is >30 mL.