Drug product:	Naropin	**SYNOPSIS**	
Drug substance(s):	Ropivacaine		
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A randomised, double-blind, multi-centre, parallel group study comparing efficacy and safety of 5 mg/ml ropivacaine and 5 mg/ml bupivacaine for spinal anesthesia in patients undergoing unilateral lower limb surgery

Study centre(s)

This study was conducted in China (7 centres).

Publications

None at the time of writing this report

Study dates		**Phase of development**
First subject enrolled	19 April, 2006	Therapeutic confirmatory (III)
Last subject completed	21 September, 2006	

Objectives

The primary objective of this study was to compare the efficacy, duration of motor block until returned to normal function in the non-operated leg after the start of injection, of ropivacaine 5 mg/ml and bupivacaine 5 mg/ml when used for spinal anesthesia in patients undergoing unilateral lower limb surgery.

The secondary objectives of the study were as follows in patients undergoing unilateral lower limb surgery with spinal anesthesia:

- To compare the efficacy of ropivacaine 5 mg/ml and bupivacaine 5 mg/ml in the duration of sensory block at dermatome level T10
- To compare the efficacy of ropivacaine 5 mg/ml and bupivacaine 5 mg/ml in the onset time of sensory block and motor block respectively

- To compare the efficacy of ropivacaine 5 mg/ml and bupivacaine 5 mg/ml in the quality of anesthesia
- To compare the efficacy of ropivacaine 5 mg/ml and bupivacaine 5 mg/ml in subject pain during surgery
- To determine the safety of ropivacaine 5 mg/ml and bupivacaine 5 mg/ml by evaluating the incidence and severity of adverse events, blood pressure, pulse rate and blood loss

Study design

This was a randomised, double-blind, parallel-group, multi-centre study comparing the efficacy and safety of 5mg/ml ropivacaine and 5mg/ml bupivacaine for spinal anesthesia in patients undergoing unilateral lower limb surgery.

Target subject population and sample size

Male or female subjects of ASA category I-II, in the age range 18-70 years, scheduled for unilateral lower limb surgery with an estimated duration < 2 hours under spinal anesthesia were enrolled.
A sample size of 100 evaluable subjects per treatment arm is requested by China State Food and Drug Administration (SFDA) for imported drug registration purpose. Considering the rate of non-evaluable subjects being 10%, the total sample size is planned to be 220 subjects. The 220 subjects will be randomised in a ratio of 1:1 to two treatment groups, with 110 in each treatment arm.
A total of 100 randomised and evaluable subjects, derived from an estimated 110 randomised subjects, were required per treatment group for more than 95% power of detecting a 60 min difference between groups in duration of motor block.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Ropivacaine 5 mg/ml in a 10-ml ampoule, single administration of 3.5 ml intrathecally, batch number was GH56; Bupivacaine 5 mg/ml in a 5-ml ampoule, single administration of 2.5 ml intrathecally, batch number was 5H04016.

Duration of treatment

Single injection

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Duration of motor block (Bromage score≥1) until return to normal motor function (Bromage score=0)
- Secondary variables:

    0 Duration of sensory block at dermatome level T10

1 Time to onset on sensory block at dermatome level T10

2 Time to onset of motor block at Bromage scores 1, 2 and 3 respectively

3 Quality of anesthesia

4 Subject pain during surgery

Safety

5 Adverse Events (AEs)

6 Blood pressure

7 Pulse rate

8 Blood loss

Statistical methods

The intention to treat (ITT) population was all subjects who had received the study treatment and had duration of motor block measured after injection. The per-protocol (PP) population included all ITT subjects without major protocol deviation. The safety population included all subjects who had received study treatment. The efficacy analysis was performed on the ITT population and the PP population as supportive validation. Analysis of primary variable, the duration of motor block, was performed using a stratified Wilcoxon rank sum test. In addition, an estimate of the difference in median duration of motor block together with 95% confidence intervals was calculated using Hodges-Lehmann estimate for Wilcoxon rank sum test. The safety analysis was performed on safety population. For all tests, center was used as a stratification variable where appropriate.

Subject population

Subject population and disposition were summarized in Table S1. In this table, demographic and baseline characteristics data are summarized from the safety population.

Table S1 Subject population and disposition

		ROPI		BUPI		Total	
Population							
N randomised (N planned)		112	(110)	109	(110)	221	(220)
Demographic characteristics P[a]							
Sex (N and % of subjects)	Male	66	(60.0)	53	(49.1)	119	(54.6)
	Female	44	(40.0)	55	(50.9)	99	(45.4)
Age (years)	Mean (SD)	41.1	(14.10)	43.3	(13.60)	42.2	(13.87)

		ROPI		BUPI		Total	
	Range	17 - 67		17 - 71		17 - 71	
Race (N and % of subjects)	Oriental	110	(100)	108	(100)	218	(100)
Baseline characteristics [b]							
BMI	Mean (SD)	22.1	(1.59)	22.1	(1.57)	22.1	(1.58)
ASA class (N and %)	I	92	(83.6)	87	(80.6)	179	(82.1)
	II	18	(16.4)	21	(19.4)	39	(17.9)
Pulse rate (beats/min)	Mean (SD)	78.1	(13.89)	77.5	(10.69)	77.8	(12.38)
Systolic BP (mmHg)	Mean (SD)	125.4	(18.80)	126.7	(18.10)	126.1	(18.42)
Diastolic BP (mmHg)	Mean (SD)	75.1	(11.96)	76.8	(12.04)	75.9	(12.00)
Disposition							
N (%) of subjects who	Completed	111	(99.1)	107	(98.2)	218	(98.6)
	Discontinued	1	(0.9)	2	(1.8)	3	(1.4)
N analysed for safety [c]		111		109		220	
N analysed for efficacy (ITT)		110		108		218	
N analysed for efficacy (PP)		107		100		207	

[ab] Data of demographic and baseline characteristics are based on the ITT population
[c] Number of subjects who took at least 1 dose of study treatment

223 patients had been enrolled and 221 had been randomised. The treatment groups were generally well balanced in demographic and baseline characteristics; there were slightly fewer women in the ropivacaine treatment group. Reasons of all discontinuations of study treatment or assessment were violation of inclusion criterion (3 cases), which were relatively rare in two treatment groups.

Efficacy results

The primary endpoint, duration of motor block (Bromage score≥1) until returned to normal motor function (Bromage score=0) of Ropi group was statistically significantly shorter than that of Bupi group in the ITT population (p=0.0000) (see Table S2). The estimated difference was more than 1 hour (65.3min) between Ropi group (178.4min) and Bupi group (245.8min) with clinical significance. Compared with the PP population, the result was similar.
In terms of key secondary efficacy results, Ropi group had a 17.8 min statistically significantly shorter (p=0.0378) duration of sensory block at dermatome level T10 (Ropi 118.5min, Bupi 128.6min). The onset time of sensory block at dermatome level T10 of two treatment groups did not have statistically significant difference (p=0.8024). Only 0.5min (Ropi 3.0min, Bupi 2.5min) difference of median onset time of motor block was found between two treatment groups, although it had statistical significance (p=0.0217). Quality of anesthesia and subject pain during surgery did not have statistically significantly difference between two treatment groups. Quality of muscle relaxation of Ropi group was superior to

Bupi group. Percentages of 'Excellent' were 91.8% in Ropi group and 81.5% in Bupi group with statistically significant difference (p=0.0112).
As bupivacaine is acknowledged as a clinically effective anesthetic for spinal anesthesia, these results suggested that ropivacaine had good clinical efficacy in having shorter duration of motor block, which was longer enough for the surgery and could bring quicker recovery of patients after surgery. At the same time, ropivacaine had shorter duration of sensory block with a better quality of muscle relaxation than bupivacaine in this study.

Table S2 Duration of motor block [a] (Bromage score≥1) until return to normal motor function (Bromage score=0) (min) (ITT analysis set)

Treatment group	% with block	N	Mean	Median	SD	Min	Q1	Q3	Max
ROPI	100	110	181.1	178.4	45.46	96	147.0	205.5	330
BUPI	100	108	248.4	245.8	67.40	115	200.4	284.8	461
p-value [b]		0.0000							
Lower 95%CL		51.0							
Difference [c]		65.3							
Upper 95%CL		78.5							

[a] Duration of motor block: starting from first motor block (Bromage score≥1) until return to normal motor function (Bromage score = 0) after the start of injection in the non-operated leg
[b] p-value: corresponds to a stratum adjusted Wilcoxon (mid)rank sum test
c Difference: Hodges-Lehmann point/confidence estimates are based on inversion of stratified rank test
CL=Confidence limit; N=Number of subject; SD=Standard Deviation

Safety results

Table S3 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	N (%) of subjects who had an adverse event in each category [a]					
	ROPI (n=111)		BUPI (n=109)		Total (n=220)	
Any adverse events	19	(17.1)	20	(18.3)	39	(17.7)
Serious adverse events	1	(0.9)	0	(0)	1	(0.5)
Serious adverse events leading to death	0	(0)	0	(0)	0	(0)
Serious adverse events not leading to death	1	(0.9)	0	(0)	1	(0.5)
Discontinuations of study treatment due to adverse events	0	(0)	0	(0)	0	(0)
Other significant adverse events	0	(0)	0	(0)	0	(0)
	Total number of adverse events					

Category of adverse event	N (%) of subjects who had an adverse event in each category [a]		
	ROPI (n=111)	BUPI (n=109)	Total (n=220)
Adverse events	23	22	45
Serious adverse events	1	0	1
Other significant adverse events	0	0	0

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

Table S4 **Number (%) of subjects with the most commonly reported [a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)**

Adverse event (preferred term)	Number (%) of subjects who had an adverse event					
	ROPI (n=111)		BUPI (n=109)		Total (n=220)	
Chills	3	(2.7)	4	(3.7)	7	(3.2)
Hypotension	3	(2.7)	4	(3.7)	7	(3.2)
Headache	4	(3.6)	2	(1.8)	6	(2.7)

[a] Events with a total frequency of ≥3% across all treatment groups are included in this table.

Overall, ropivacaine was well tolerated. A similarly low frequency, duration and intensity of adverse events were reported in both treatment arms. The most common adverse events (chills, hypotension, headache) reflected the expected physiological effects of surgery, intrathecal administration of a local anesthetic and spinal punctuation procedure itself. The most common adverse events had low frequencies ≤ 4% and were typically mild or moderate (only 1 case of severe chill in Ropi group). Serious adverse events were rare (1 case of ectomy of fibrosarcoma on the leg led to prolongation of existing hospitalisation in the Ropi group) and not considered treatment-related. There was no case of discontinuation of study treatment due to adverse events in both groups. The changes in vital signs including pulse rate and blood pressure in this study reflected the expected physiological effects of intrathecal administration of a local anesthetic. Blood losses in these two groups were the same and insignificant (median 40ml). Safety data from this study did not suggest any difference in the safety profile of the two drugs.