META-ANALYSIS

The Effect of Scalp Nerve Block on Postoperative Analgesia and Stress Response in Patients Undergoing Craniotomy: A Meta-Analysis

Xiaojing Wei, MM; Zhongqiang Liu, BM; Chong Liu, BM; Shukai Li, BM; Jing An, BM; Zhixue Wang, MM

ABSTRACT

Objective • To evaluate the effect of scalp nerve block (SNB) on postoperative analgesia and stress response in patients undergoing craniotomy by meta-analysis.

Methods • PubMed, Embase, Cochrane Library, CNKI, and Wanfang databases were searched for randomized controlled trials involving SNB for elective craniotomy under general anesthesia from inception to August 1, 2022. Meta-analysis was performed using RevMan 5.4 and Stata MP17.0. Based on scalp block operation time (preoperative block, postoperative block), different control groups (no block, normal saline), local anesthetic types (bupivacaine, levobupivacaine, ropivacaine), the postoperative pain score at different time points was analyzed by subgroup analysis.

Results • 23 studies involving 1515 patients were included. The combined results showed that SNB could significantly reduce the pain scores at all time points compared with the control group ($P < .05$). Subgroup analysis showed that the analgesic effect of preoperative scalp nerve block was better than that of postoperative block, and the effect of ropivacaine and levobupivacaine was better than bupivacaine. SNB could reduce morphine consumption within 48 hours after surgery (SMD = -1.51, 95% CI -2.80 -0.21, $P = .02$, $I^2 = 89\%$). The first rescue analgesia time was significantly longer in the SNB group than the control group (SMD = 0.57, 95% CI 0.16-0.99, $P = .01$, $I^2 = 68.76\%$). Compared with the control group, the levels of postoperative angiotensin, intraoperative blood glucose, and both intraoperative and postoperative cortisol levels were significantly decreased ($P < .05$). SNB can inhibit hemodynamic changes caused by surgical stimulation and effectively reduce the incidence of postoperative nausea and vomiting (RR = 0.71, 95% CI 0.51~0.97, $P = .03$).

Conclusion • Scalp nerve block is an effective analgesic that reduces pain within 48 hours after craniotomy. It effectively inhibit the stress response caused by surgical stimulation, stabilize hemodynamics, and reduce the incidence of postoperative nausea and vomiting. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

The pain after craniotomy is most serious within 48 hours after craniotomy.[1] About 60% of 80% of the patients experienced pain after craniotomy, of which 2/3 showed moderate to severe pain.[2] The line of treatment used for pain management after craniotomy is often insufficient,[3,4] which will cause sympathetic excitement, strong stress response, increased blood pressure and heart rate, resulting in increased intracranial pressure. Even the procedure of intracranial or secondary surgery greatly increases the incidence of adverse outcome.[1] In the past, the use of opioid analgesia after postoperative analgesia were shown to slow down the recovery of cognitive function, along with side effects such as hyperalgesia, nausea, and constipation.[3]

Currently, scalp nerve block (SNB) is used as the main analgesic method. SNB is combined with non-opioid drugs having different mechanisms of action to maximize the analgesic effect. Traumatic stimulation, such as surgery, acts on peripheral nerve pain receptors and generates nerve impulses that are transmitted to spinal dorsal horn neurons through Aδ and C fibers, and then pain is generated after uploading and integration. SNB can cut off this pathway. Effective postoperative analgesia can reduce complications and reduce mortality.[5] With the continuous publication of clinical randomized controlled trials, the analgesic duration and

Table 1. Characteristics of Included Studies

			Experiment group			Control group					
Study	**Time**	**Scale**	**n1**	**Volume (ml)**	**Anesthetics**	**n2**	**Volume (ml)**	**Intervention**	**Measurement time(hour)**	**Analgesic**	**Complication**
Rigamonti 2020	Postoperation	VAS 1-100	41	20 ml	0.5%bupivacaine +1:200,000 epinephrine	44	20 ml	saline+1:200,000 epinephrine	1/2/4/8/12/18/24/48 h	hydromorphone	PONV
Nguyen 2001	Postoperation	VAS 1-10	15	20 ml	0.75%ropivacaine	15	20 ml	saline	4/8/12/16/20/24/48 h	codeine	No report
Bala 2006	Postoperation	NRS 1-100	20	20 ml	0.5%bupivacaine+1:400,000 epinephrine	20	20 ml	saline+1:400,000 epinephrine	0.5/1/2/4/6/8/12 h	diclofenac, tramadol	no
Gazoni FM2008	Preoperation	VAS1-10	14	/	0.5%ropivacaine	16	/	No block	1/2/4 h	morphine	PONV
Gaudray 2020	Preoperation	NRS1-10	46	20–25 ml	0.75%ropivacaine	88	/	No block	PACU/8/16/24/32/40/48/48 h	morphine	PONV
Skutulien2022	Postoperation	VAS 1-100	47	20 ml	0.25% bupivacaine+1% lidocaine+1:200,000 epinephrine	47	/	No block	1/3/6/24h	ketorolac, paracetamol,	no
Carella 2021	Preoperation	VAS 1-10	30	30 ml	0.33%levobupivacaine	30	30 ml	saline	1/3/6/24/48 h	morphine	No report
Hwang 2015	Postoperation	NRS 1-100	23	7 ml	0.75%levobupivacaine+ 1:200,000 epinephrine	23	7 ml	saline	1/2/4/8/12/16/24/48/72 h	fentanyl-based PCA	PONV, fever
Tuchinda 2010	Preoperation	VAS 1-10	21	10.5-14 ml	0.5%bupivacaine+1:200,000 epinephrine	20	10.5-14 ml	saline+1:200,000 epinephrine	0.5/1/1.5/2/6/12/24 h	morphine	PONV
Geze S2008	Preoperation	/	15	20 ml	0.5% bupivacaine	15	/	No block	/	/	No report
Yang X 2019	Preoperation	VAS 1-10	18	15 ml	0.75% ropivacaine	17	/	No block	2/4/8/12/24/48 h	oxycodone	PONV, fever
Yang Y 2020	Preoperation	VAS 1-10	22	8 ml	0.5% ropivacaine	22	8 ml	saline	2/4/6/24h	dezocine	PONV
Wang G 2009	Preoperation	/	20	16 ml	0.5%ropivacaine+ 1:200,000epinephrine	20	16 ml	saline+1:200,000 epinephrine	/	/	No report
Liu F 2014	Preoperation	VAS 1-10	20	6-8 ml	0.5%ropivacaine	20	/	No block	2/6/24/48 h	Parecoxib inj	PONV
Pang D 2015	Preoperation	VAS 1-10	40	19 ml	0.596%ropivacaine	40	/	No block	0.5 h/2 h/6 h/12 h/24 h/48 h	/	No report
Tong-tong Z2016	Preoperation	VAS 1-10	18	6-8 ml	0.5%ropivacaine	18	/	No block	2/6/24/48 h	/	No report
Luo H 2016	Preoperation	VAS 1-10	30	10.5-14 ml	0.5%ropivacaine	30	10.5-14 ml	saline	2/6/12 h	/	Drowsiness
Sun Z 2018	Preoperation	VAS 1-10	23	28 ml	0.5%ropivacaine	23	/	No block	2/6/12/24 h	/	PONV
Li D 2019	Preoperation	VAS 1-10	150	6-8 ml	0.5%ropivacaine	150	/	No block	2/24/48 h	/	No report
Cheng G 2020	Preoperation	VAS 1-10	20	2-6 ml	1%lidocaine+0.33% ropivacaine	20	/	No block	0.5/1 h	/	No report
Zhao Y 2021	Preoperation	/	30	18 ml	0.6%ropivacaine	30	/	No block	/	/	No report
Liu Ge 2021	Preoperation	VAS 1-10	43	12 ml	0.5% ropivacaine	43	/	No block	2/6/12/24/48 h	/	Dizzy, PONV, respiratory depression
Zhu Y 2021	Preoperation	/	30	22 ml	0.4%ropivacaine	30	/	No block	/	/	No

intensity of SNB and its inhibitory effect on stress response remain unclear during craniotomy. Therefore, this study attempts to conduct a meta-analysis to systematically review the literature and provide a reference for clinical programs.

METHODS

Search Methods

Our meta-analysis is based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting standards. The PRISMA Guideline is a systematic review and meta-analysis reporting standard developed by the PRISMA Group, consisting of a list of 27 entries and a four-stage flow chart (consisting of search, preliminary screening, inclusion, and synthesis).

Comprehensive search was conducted in the PubMed, Embase, Cochrane Library, China knowledge Network, and Wanfang databases. The key English search words used are "craniotomy", "neurosurgery", and "scalp nerve block". The retrieval date was set from the establishment of the database to August 1, 2022, the retrieval languages are English and Chinese, and the retrieval method combining subject headings and free words were adopted. References of published literature and meta-analyses were manually searched. The detailed search strategy is shown in Appendix 1.

Eligibility Criteria

Inclusion criteria: (1) patients undergoing elective craniotomy, aged 18-93 years old, American Society of Anesthesiologists (ASA) I~IV grade, regardless of sex; (2) the type of study design is a clinical randomized controlled trial (RCT); (3) the intervention was SNB in the intervention group, and saline block or no block in the control group; (4) both the intervention group and the control group were given general anesthesia with endotracheal intubation; (5) postoperative pain score (visual analog scale (VAS) or numeric rating scale (NRS)), or intraoperative hemodynamic parameters, anesthetic drug consumption, stress response, and other indicators were reported in the results.

Exclusion criteria: (1) surgery for drilling and drainage; (2) the study population is simple elderly patients; (3) second craniotomy, severe hepatorenal dysfunction, mental disorder, long-term use of analgesics; (4) Glasgow coma score less than 14 (unable to answer questions correctly); (5) the report of the results was incomplete, and the authors were still unable to obtain complete data after contacting the authors; (6) identify or suspect allergy to local anesthetics. The basic characteristics of the included studies are shown in Table 1.

Study Selection and Data Collection

Literature screening and data extraction: Literature screening and data extraction were carried out independently by two researchers, and differences were discussed or decided by the third researcher. The main contents of data extraction include: author, publication year, country, ASA classification, operation time of nerve block, number of intervention group and control group, type and volume of local anesthetics, postoperative rescue analgesics and adverse reactions. The pain scores at each time point after operation (including digital

analog scale NRS and VAS), different pain scales were transformed into VAS (1-10 cm);[6,7] 24-hour and 48-hour morphine consumption, Different types of analgesics need to be converted into equivalent doses of morphine;[8] postoperative first rescue analgesia time; hemodynamic parameters include (mean arterial pressure (MAP) and hear rate (HR)); stress response indicators include angiotensin II, cortisol, blood sugar; the number of people with nausea and vomiting.

Risk of Bias Assessment

ReviewMan5.4 was used to draw a risk bias assessment chart. Two independent researchers used the Cochrane risk bias assessment system to evaluate the quality of the included literature. Cochrane bias risk assessment tool is a common tool used by meta-analysis researchers to evaluate the quality of randomized controlled trials, and it is a unique function of RevMan. Items assessed included random sequence generation, allocation concealment, blinding of investigators and outcome raters, completeness of outcome data, selective reporting of outcome measures, and other biases.

Statistical Analysis

Statistical analysis: Data were processed using ReviewMan5.4 and Stata MP17.0. Continuous variables are described by standardized mean difference (SMD) and 95% confidence interval (CI), and binary variables are described by relative risk ratio (RR). The heterogeneity between studies was evaluated by the I^2 value. If $I^2 \leq 50\%$, there was no heterogeneity, and a fixed effect model was selected; if $I^2 > 50\%$, it was considered to have significant heterogeneity, random effect model was selected. Subgroup analysis, sensitivity analysis, and Gilbrath diagram were used to find the source of heterogeneity. For the outcome indicators included in 10 or more studies, meta regression was used to find the sources of heterogeneity. Publication bias detection can be performed Egger's test and by drawing a funnel plot. $P < .05$ was considered statistically significant.

RESULTS

Results of the Search

Literature search results: 1074 literatures were obtained in the initial search, and 23 literatures were finally selected after screening, including 12 English literatures[9-20] and 11 Chinese literatures.[21-31] A total of 1517 patients, including 736 in the intervention group and 781 in the control group, were included in the screening flow chart as shown in Figure 1. The risk assessment of bias is shown in Figure 2.

Characteristics of Included Studies

Among all the included literatures, 9 literatures in the control group were normal saline (with or without epinephrine) and 14 literatures were not blocked; head nerve block using bupivacaine in 4 literatures, bupivacaine combined with lidocaine in 1 literature, levobupivacaine in 2 literatures, ropivacaine in 15 literatures, ropivacaine combined with lidocaine in 1 literature (local anesthetic with or without

Figure 1. Study Flow Chart Based on PRISMA Guideline

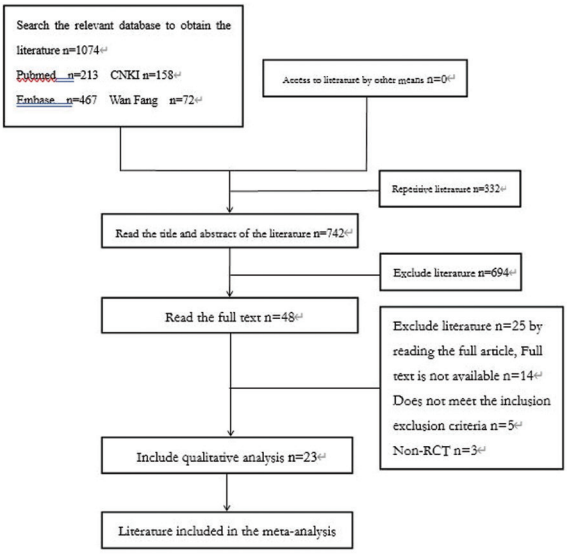


Figure 2. Risk of Bias Assessment Summary

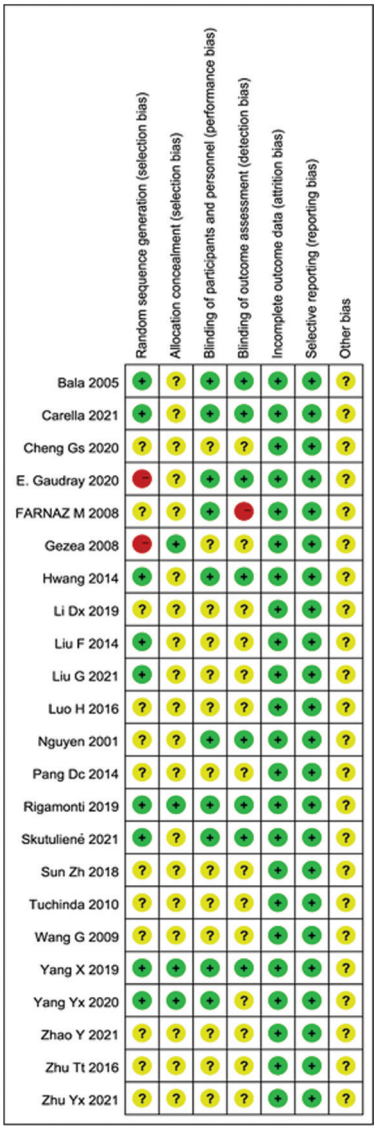


Figure 3. Pain scores 0.5 h after surgery

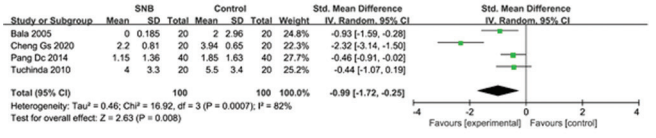


Figure 4. Pain Scores 1 h After Surgery

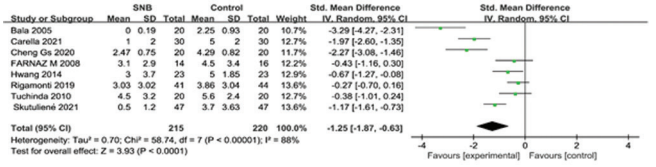


Figure 5. Pain Scores 2 h After Surgery

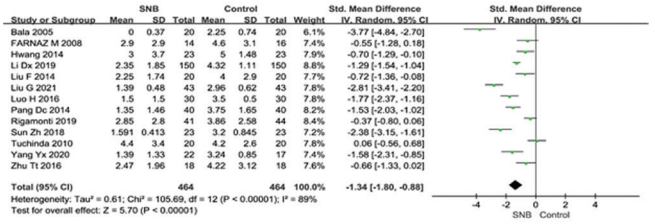


Figure 6. Pain Scores 4 h After Surgery

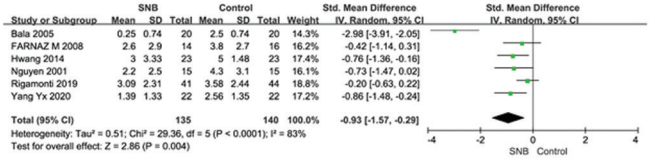


Figure 7. Pain Scores 6 h After Surgery

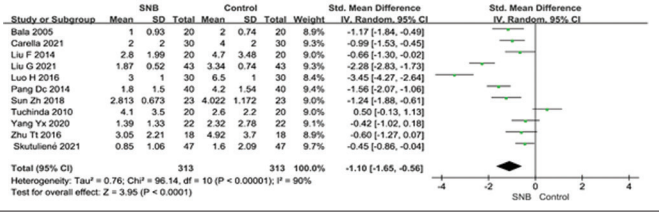


Figure 8. Pain Scores 8 h After Surgery

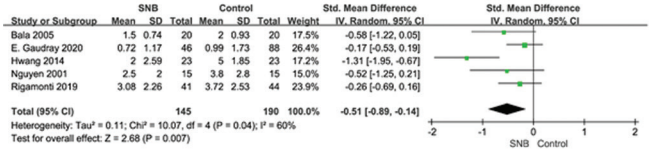


Figure 9. Pain Scores 12 h After Surgery

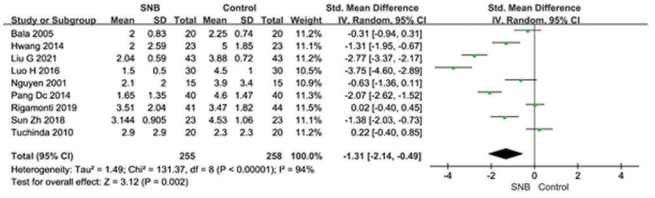


Figure 10. Pain Scores 24 h After Surgery

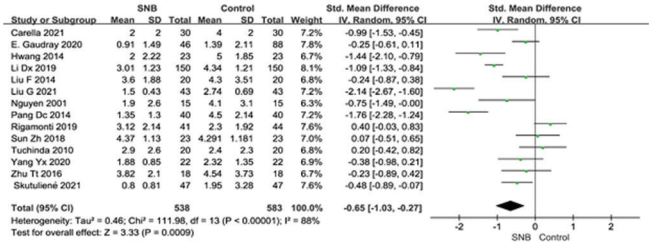


Figure 11. Pain Scores 48 h After Surgery

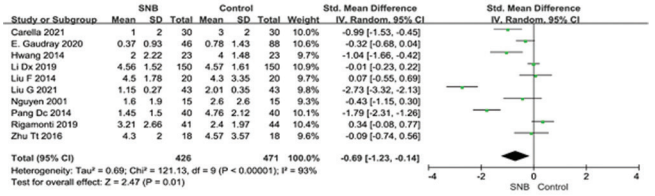


Figure 12. Morphine Consumption Within 24 h of Surgery

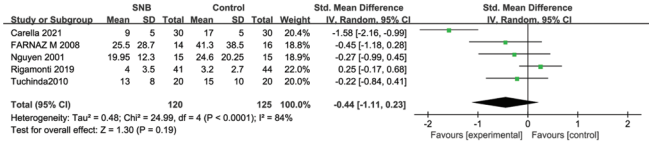


Figure 13. Morphine consumption Within 48 h of Surgery

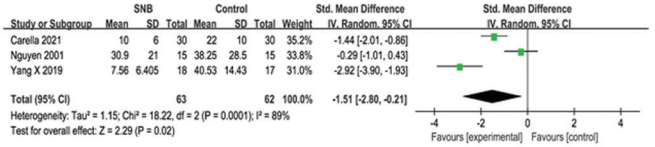


Figure 14. First Rescue Analgesia Time After Surgery

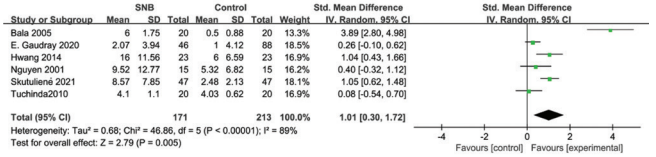
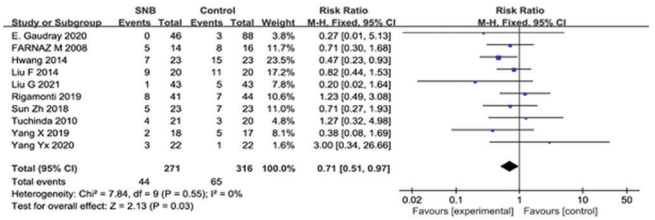


Figure 15. PONV After Surgery



epinephrine). There were 18 literatures about head nerve block before operation, and 5 literatures about head nerve block before awakening after operation. There were 16 literatures using VAS scale to evaluate pain and 3 literatures using NRS scale. 2 literatures reported angiotensin content, 4 literatures reported blood glucose levels, and 3 literatures reported cortisol. 10 literatures reported intraoperative MAP and HR changes. There were 5 literatures in the three-arm test, of which three were SNB and scalp infiltration compared with the control group; two were different concentrations of ropivacaine compared with the control group, we extracted 0.5% ropivacaine group and control group information. The results of 3 literatures were reported as median and interquartile range, which were converted according to the corresponding formula (If the sample size of the study is large and the data distribution is close to normal distribution, the interquartile interval is approximately 1.35×SD). Results from 3 literatures are reported in graph form.

Table 2. Subgroup Analysis According to Different Blocktime

	Preoperation SNB					Postoperation SNB					Meta
Time	n	SMD	95% CI	*P* value	I^2	n	SMD	95% CI	*P* value	I^2	regression
0.5hVAS	3	-1.03	-2.06~-0.00	.05	88.00%	1	-0.93	-1.59~-0.28	.005	NA	*P* = .927
1hVAS	4	-1.25	-2.22~-0.29	.01	87.00%	4	-1.26	-2.18~-0.34	.008	91.00%	*P* = .928
2hVAS	10	-1.32	-1.79~-0.85	<.00001	86.00%	3	-1.53	-3.05~0.00	.05	94.00%	*P* = .844
4hVAS	2	-0.67	-1.14~-0.20	.005	0.00%	4	-1.11	-2.09~-0.12	.03	89.00%	*P* = .558
6hVAS	9	-1.18	-1.85~-0.51	.0006	91.00%	2	-0.76	-1.45~-0.06	.03	68.00%	*P* = .612
8hVAS	1	-0.17	-0.53~0.19	.35	NA	4	-0.64	-1.10~-0.18	.006	58.00%	*P* = .311
12hVAS	5	-1.93	-1.36~-0.71	.002	95.00%	4	-0.53	-1.12~0.06	.08	75.00%	*P* = .062
24hVAS	10	-0.70	-1.15~-0.25	.002	89.00%	4	-0.54	-1.29~0.22	.16	87.00%	*P* = .716
48hVAS	7	-0.83	-1.53~-0.12	.02	93.00%	3	-0.35	-1.23~0.53	.43	85.80%	*P* = .470

Abbreviaitions: n, Number of trails pooled; CI, confidence interval; SMD, stand mean difference.

Table 3. Subgroup Analysis According to Different Control Group

	No block					Saline					Meta
Time	n	SMD	95% CI	*P* value	I^2	n	SMD	95% CI	*P* value	I^2	regression
0.5hVAS	2	-1.36	-3.18~0.46	.14	93.00%	2	-0.68	-1.16~-0.19	.006	13.00%	*P* = .496
1hVAS	3	-1.27	-2.15~-0.39	.005	82.00%	5	-1.26	-2.18~-0.33	.008	91.00%	*P* = .975
2hVAS	7	-1.42	-1.96~-0.87	<.00001	89.00%	6	-1.28	-2.13~-0.43	.003	91.00%	*P* = .764
4hVAS	1	-0.42	-1.14~0.31	.26	NA	5	-1.04	-1.79~-0.28	.007	86.00%	*P* = .513
6hVAS	6	-1.13	-1.73~-0.54	.0002	86.00%	5	-1.08	-2.19~0.02	.06	93.00%	*P* = .918
8hVAS	1	-0.17	-0.53~0.19	.35	NA	4	-0.64	-1.10~-0.18	.006	58.00%	*P* = .311
12hVAS	3	-2.08	-2.84~-1.33	<.00001	79.00%	6	-0.93	-1.89~0.04	.06	93.00%	*P* = .128
24hVAS	8	-0.77	-1.27~-0.28	.002	90.00%	6	-0.48	-1.08~0.12	.12	84.00%	*P* = .451
48hVAS	6	-0.8	-1.60~0.00	.05	95.00%	4	-0.51	-1.25~0.22	.17	85.00%	*P* = .648

Abbreviaitions: n, Number of trails pooled; CI, confidence interval; SMD, stand mean difference.

Table 4. Subgroup Analysis According to Different Anesthetics

	Ropivacaine					Bupivacaine					Levobupivacaine					Meta
Time	SMD	95% CI	n	I^2	*P* value	SMD	95% CI	n	I^2	*P* value	SMD	95% CI	n	I^2	*P* value	regression
0.5hVAS	-0.46	-0.91~-0.02	1	NA	.04	-0.68	-1.16~-0.19	2	13.00%	.006						
1hVAS	-0.43	-1.16~0.30	1	NA	.25	-1.25	-2.72~0.22	3	94.00%	.1	-1.32	-2.60~-0.04	2	89.00%	.04	
2hVAS	-1.47	-1.91~-1.04	9	82.00%	<.00001	-1.28	-2.96~0.39	3	95.00%	.13	-0.7	-1.29~-0.10	1	NA	.02	*P* = .469
4hVAS	-0.69	-1.09~-0.29	3	0.00%	.0007	-1.56	-4.28~1.16	2	96.00%	.26	-0.76	-1.36~-0.16	2	NA	.01	
6hVAS	-1.44	-2.16~-0.73	7	89.00%	<.00001	-0.33	-1.96~1.31	2	92.00%	.70	-0.99	-1.53~-0.45	1	NA	.70	*P* = .127
8hVAS	-0.24	-0.56~0.08	2	0.00%	.14	-0.36	-0.72~-0.01	2	0.00%	.04	-1.31	-1.95~-0.67	1	NA	<.0001	
12hVAS	-2.11	-3.03~-1.18	5	90.00%	<.00001	-0.01	-0.32~0.30	3	0.00%	.95	-1.31	-1.95~-0.67	1	NA	<.0001	*P* < .001
24hVAS	-0.76	-1.23~-0.29	9	88.00%	.001	0.34	-0.02~0.69	2	0.00%	.06	-1.18	-1.62~-0.74	2	10.00%	<.00001	*P* = .135
48hVAS	-0.75	-1.46~-0.03	7	94.00%	.04	0.34	-0.08~0.77	1	NA	.12	-1.01	-1.42~-0.60	2	0.00%	<.00001	*P* = .452

Abbreviaitions: n, Number of trails pooled; CI, confidence interval; SMD, stand mean difference.

Effects of Interventions

Main outcome indicators: Postoperative pain score; Morphine consumption at 24 hours and 48 hours after surgery.

According to different time points, we extracted and analyzed the postoperative pain scores at 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h, and 48 h. Among them, 4 literatures were included in 0.5 h, more than 10 literatures were included in 2 h, 6 h, 24 h, and 48 h, and 5-9 literatures were included in other time points. The results showed that at each time point, the postoperative pain score was significantly lower than that in the control group. The results of meta-analysis were: At 0.5 h after operation: (*SMD* = -0.99, 95% CI -1.72~-0.25, *P* = .008, I^2 = 82%); at 1 h after operation: (*SMD* = -1.25, 95% CI -1.87~-0.63, *P* < .0001, I^2 = 88%); at 2 h after operation: (*SMD* = -1.34, 95% CI -1.80~-0.88, *P* < .0001, I^2 = 89%); at 4 h after operation: (*SMD* = -0.93, 95% CI -1.57~-0.29, *P* = .004, I^2 = 83%); at 6 h after operation: (*SMD* = -1.10, 95% CI -1.65~-0.56, *P* < .0001, I^2 = 90%); at 8 h after operation: (*SMD* = -0.51, 95% CI -0.89~-0.14, *P* = .007, I^2 = 60%); at 12 h after operation (*SMD* = -1.31, 95% CI -2.14~-0.49, *P* = .002, I^2 = 94%); at 24 h after operation (*SMD* = -0.65, 95% CI -1.03~-0.27, *P* = .0009, I^2 = 88%); at 48 h after operation (*SMD* = -0.69, 95% CI -1.23~-0.14, *P* = 0.01, I^2 = 93%), After excluding studies with high heterogeneity by sensitivity analysis, 1 h (*SMD* = -0.41, 95% CI -0.69~-0.13, *P* = .005, I^2 = 0%), 2 h (*SMD* = -1.05, 95% CI -1.36~-0.74, *P* < .00001, I^2 = 55%), 4 h (*SMD* = -0.53, 95% CI -0.80~-0.25, *P* = .0001, I^2 = 6%), 6 h (*SMD* = -0.75, 95% CI -1.01~-0.50, *P* < .00001, I^2 = 25%), 8 h (*SMD* = -0.30, 95% CI -0.53~-0.06, *P* = .01, I^2 = 0%), 12 h (*SMD* = -1.61, 95% CI -2.11~-1.12, *P* < .00001, I^2 = 50%), 24 h (*SMD* = -0.45, 95% CI -0.65~-0.24, *P* < .0001, I^2 = 9%), 48 h (*SMD* = -0.47, 95% CI -0.82~-0.12, *P* = .009, I^2 = 57%), The heterogeneity decreased, and there was no change before and after elimination. However, sensitivity analysis showed that at 0.5 h after surgery, the results changed after the study of Bala,[11] was excluded, suggesting that the results were unstable.

Acorrding to different scalp block times (preoperative block, postoperative block), different control groups (no block, normal saline), different kinds of local anesthetics (bupivacaine, levobupivacaine, ropivacaine), subgroup analysis was performed on the pain scores at each time point. When the number of included literatures exceeded 10, we performed a meta-regression analysis. The results are shown in Table 2-4.

According to the subgroup analysis of different block time, the analgesic effect of scalp block conducted when surgery finished lasted until 8 hours after operation, and the

Table 5. Blood Glucose, Angiotensin II, Cortisol Levels at Different Time

	Blood glucose					Angiotensin II					Cortisol				
Time	**n**	**SMD**	**95% CI**	***P* value**	I^2	**n**	**SMD**	**95% CI**	***P* value**	I^2	**n**	**SMD**	**95% CI**	***P* value**	I^2
Before surgery	4	0.04	-0.26~0.35	.77	31.34%	2	0.06	-0.43~0.55	.82	54.53%	5	-0.09	-0.32~0.15	.47	0.00%
Pin	2	-0.87	-1.90~0.15	.1	85.45%	/					/				
Incision	4	-1.39	-2.54~-0.24	.02	93.76%	2	-0.66	-2.02~0.71	.35	93.32%	3	-0.65	-1.14~-0.17	.01	65.34%
Craniotomy	3	-1.64	-2.89~-0.38	.01	92.41%	/					/				
Intraoperation	2	-1.87	-2.31~-1.43	<.001	17.71%	2	-1.36	-3.21~0.50	.15	95.54%	4	-1.1	-1.81~-0.39	<.001	82.64%
Surgery finished	3	-0.88	-2.85~1.09	.38	97.35%	2	-1.77	-2.16~-1.38	<.001	0.00%	3	-0.94	-1.43~-0.45	<.001	64.15%

Abbreviaitions: n, Number of trails pooled; CI, confidence interval; SMD, stand mean difference.

Table 6. Hemodynamics at Different Time (MAP/HR)

	HR					MAP				
Time	**n**	**SMD**	**95% CI**	***P* value**	I^2	**n**	**SMD**	**95% CI**	***P* value**	I^2
Pin	7	-1.12	-1.73~-0.50	.0004	89.00%	5	-1.71	-2.77~-0.64	.002	93.00%
Incision	9	-0.92	-1.48~-0.36	.001	91.00%	7	-1.33	-1.74~-0.91	<.00001	72.00%
Craniotomy	3	-1.11	-2.34~0.11	.07	93.00%	2	-1.19	-1.99~-0.39	.004	72.00%
Surgery finished	5	-1.28	-2.14~-0.42	.004	92.00%	4	-1.21	-1.70~-0.72	<.00001	68.00%

Abbreviaitions: n, Number of trails pooled; CI, confidence interval; SMD, stand mean difference.

analgesic effect of SNB administered before operation lasted until 48 hours after operation, the results are shown in Table 2. Subgroup analysis of pain scores at each time point was performed according to different control measures, when SNB was compared with no block, the difference persisted up to 24 hours after operation; when SNB was compared with normal saline block, .statistical significance was reached 8 hours after the operation, indicating that the normal saline block also has a potential analgesic effect (Table 3). From the subgroup analysis of different local anesthetics, it was revealed that there were significant differences in pain scores between ropivacaine group (except 8 h) and levobupivacaine group at each time point, while bupivacaine only showed significant difference at 0.5 h and 8 h after operation. The results are shown in Table 4. The result of meta-regression analysis at 12 hours after operation (was $P < .001$) indicated that the type of local anesthetic was the source of heterogeneity at this time point.

24-hour morphine consumption is (*SMD* = -0.44, 95% CI -1.11~0.22, $P = .19$, $I^2 = 84\%$). Sensitivity analysis suggested that the studies of Rigamonti,[9] Carella,[13] etc. were the main source of heterogeneity, and the combined results after exclusion were as follows: (*SMD* = -0.30, 95% CI -0.70~0.09, $P = .14$, $I^2 = 0\%$).Before and after excluding the studies that caused significant heterogeneity, the confidence intervals in the results all crossed zero, and the differences were not statistically significantThree studies[10,13,15] reported morphine consumption 48 hours after surgery (*SMD* = -1.51, 95% CI -2.80~-0.21, $P = .02$, $I^2 = 89\%$). Sensitivity analysis was performed and the results changed after Nguyen was excluded, suggesting that the results were unstable.

Secondary Outcome Indicator

The first postoperative rescue analgesia time was defined as the time from the end of the operation to the patient's first request for the use of analgesics, and the result was (*SMD* = 1.01, 95% CI 0.30~1.72, $P = .005$, $I^2 = 89\%$). After sensitivity analysis, the study excluding Bala,[11] was merged again, and the result was (*SMD* = 0.91, 95% CI 0.54~1.27, $P < .00001$, $I^2 = 20\%$). Heterogeneity was found to decrease, and the difference before and after sensitivity analysis was statistically significant.

Changes in perioperative blood glucose, angiotensin, and cortisol levels were analyzed. These three indicators are stress hormones that indicate the body's neuroendocrine response to harmful stimuli. Compared with the control group, there was no significant difference in the levels of cortisol, blood glucose, and angiotensin II between the SNB group and the control group, indicating that the baseline was comparable. There was a statistically significant difference in blood sugar levels between scalp incision, bone craniectomy, and intraoperative blood sugar. Sensitivity analysis was used to find the studies that caused high heterogeneity, data were combined again, and the results showed that the intraoperative blood glucose level in the intervention group was lower than that in the control group, and the difference was still statistically significant; The level of angiotensin II at the end of operation was significantly lower in the intervention group than that in the control group, and the results of sensitivity analysis showed that the results were stable and reliable. The levels of plasma cortisol in scalp incision, during and after operation were significantly lower in the intervention group than that in the control group. After the study contributing to the heterogeneity was eliminated, Re-merge the data，the cortisol level during and after operation was lower in the SNB group than that in the control group, and the results showed that the difference was still statistically significant (Table 5).

The changes in MAP and HR were assessed at each time point in perioperative period compared with the reference baseline. The results of meta-analysis showed that SNB could inhibit the increase of MAP at the time of pin, incision, craniotomy, and the surgery finished, and also inhibit the increase of HR at the time of pin, incision and surgery finished, but there is no statistical difference in the change of HR at the time of craniotomy compared with the control group. The results are shown in Table 6.

Incidence of postoperative nausea and vomiting (PONV): (*RR = 0.71, 95% CI 0.51~0.97, P = .03, I^2 = .00%*). Compared to the control group, SNB can reduce the incidence of postoperative nausea and vomiting.

Assessment of Publication Bias

The pain score 2 hours after the operation was included in 13 literatures, and the incidence of PONV was included in 10 literatures, and funnel plots were made with these two items, as shown in Figure 16 and 17. Egger test results $P = .0651$, $P = .8772$, The premise of effective detection of publication bias is that the number of studies included in a certain indicator is not less than 10. StataMD17.0 can complete the production of funnel diagram and egger test.

Figure 16. Funnel Plot of Pain Scores 2 h After Surgery

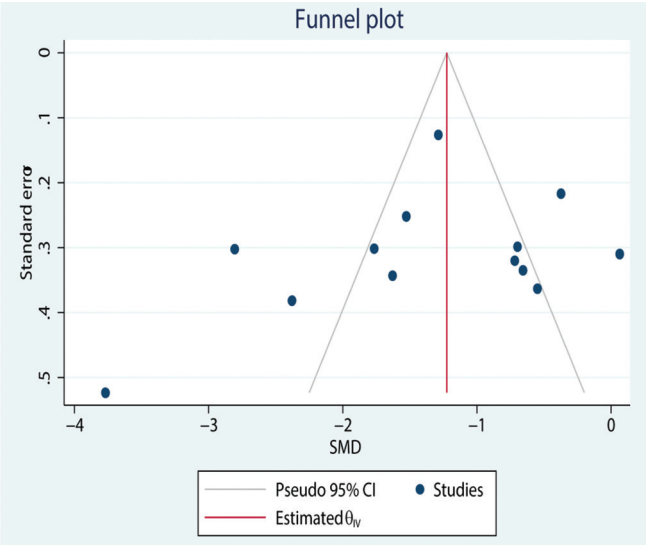
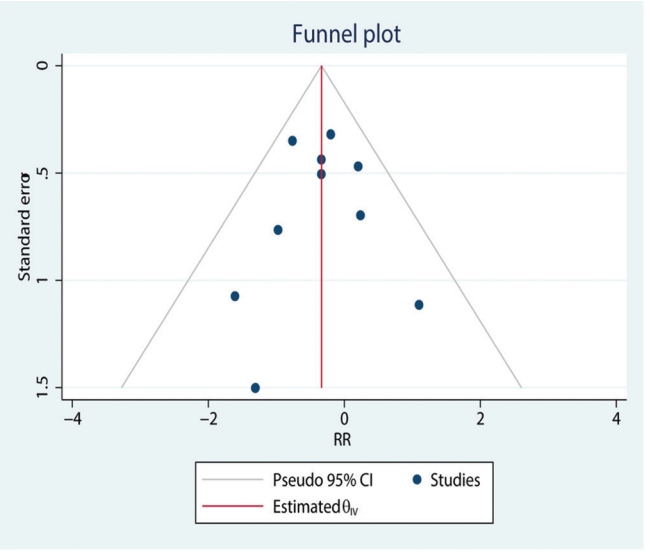


Figure 17. Funnel Plot of PONV



The funnel chart is a qualitative analysis with strong subjectivity, and the Egger test is a quantitative analysis ($P \leq .05$ has statistical significance). The combination of the two can better explain whether there is publication bias. The original data were input into Stata software, the model was created in the meta-analysis module, and the funnel plot and corresponding *P* values were obtained by performing corresponding operations in the publication bias plate. The points on both sides of the reference lines in Figures 16 and 17 are roughly symmetrical, and the *P* values of the Egger test results are both greater than .05, so there is no obvious publication bias.

DISCUSSION

Summary of Main Results

By increasing the number of studies included, the effect of SNB on postoperative analgesia in patients undergoing craniotomy was discussed comprehensively. The results showed that SNB could relieve pain effectively within 48 hours after craniotomy. The duration of continuous analgesia of scalp block before operation was longer than that of scalp block at the end of operation, lasts 48 hours and 8 hours, respectively. Although the heterogeneity was high, sensitivity analysis showed that the results were stable and would not be altered by exclusion of a study. The possible reason for this is that the preoperative block is in the range of preemptive analgesia, and the mechanism of preemptive analgesia is to prevent tissue damage and reduce stress and inflammation[32] to achieve the purpose of pain relief. According to the different types of local anesthetics, our subgroup analysis showed that ropivacaine and levobupivacaine had longer duration of postoperative analgesia and better effect than bupivacaine. SNB could not reduce 24-hour morphine consumption, and the results were stable; 48-hour morphine consumption was also higher than that of the control group, but the results were unstable due to lesser number of literatures included and the high heterogeneity. SNB can inhibit the surgical stress response. The main indicators are cortisol, blood glucose, and angiotensin II. There is no statistical difference in their preoperative levels, but the levels of blood glucose and cortisol during operation and angiotensin and cortisol after operation are significantly lower in the intervention group than that of the control group. Sensitivity analysis shows that the results are stable, indicating that SNB can inhibit the stress response. SNB can stabilize intraoperative hemodynamics and reduce the incidence of PONV.

Agreements and Disagreements with Other Studies or Reviews

According to the systematic review published by Darmawikarta et al.,[33] in 2019, there is only limited evidence to prove that SNB can reduce the dosage of opioids after operation. A meta-analysis published by Guilfoyle et al.[34] in 2013 believed that SNB was effective within 8 hours after surgery, and subgroup analysis was conducted according to different block time. The analgesic effect lasted up to 12 hours after surgery, and it could reduce the consumption of morphine at 24 hours after surgery, which was quite different from our results. The meta-analysis published by Wardhana et al.[35] in 2019 showed that the analgesic effect of SNB was only effective within 6 hours after operation. Subgroup analysis showed that the analgesic effect of preoperative block was slightly better than that of postoperative block, and there was only uncertain evidence that SNB could reduce morphine consumption 24 hours after operation. Nathan[3] also believes that if SNB is performed after surgery, the noxious stimulation at this time can lead to the occurrence of inflammation and stress response, and nerve block analgesia at this time cannot be effective postoperative analgesia for pain.

In the study we included ropivacaine hydrochloride and ropivacaine mesylate, both of which change their physical and chemical properties but have the same pharmacological effects.[36] Ropivacaine has low fat solubility and can produce separation of motor nerve and sensory nerve anesthetic effects.[37] Levobupivacaine is also an amide-based local anesthetic but it is

more lipid soluble than ropivacaine.[38] We believe that ropivacaine and levobupivacaine play a similar role in postoperative analgesia after craniotomy, which is consistent with the results of Zhang Shan and Peduto.[39,40] As a long-acting amide local anesthetic, the effect of bupivacaine can last up to 4-6 hours but bupivacaine is highly toxic to the heart, so it is necessary to pay attention to the dosage when using it, and also it should not accidentally enter the blood vessels. Mengqiang Luo et al.[41] published a reticular meta-analysis in 2022 that compared SNB with ropivacaine to other methods, and showed that the former can have a better postoperative analgesic effect, which is consistent with our conclusion.

The mechanism via which SNB can inhibit stress response is that SNB blocks the flow of sodium ions into the nerve fiber cell membrane through local anesthetics, and blocks the transmission of pain to the center from the nerve root level. Furthermore, it inhibits the production of sympathetic excitement and inflammatory mediators caused by pain stimulation, and blocks the vicious circle between pain and stress response. Scalp nerves inhibit the reactivity of the sympathetic-hypothalamic-adrenal axis, thereby inhibiting cortisol secretion, inhibiting gluconeogenesis, and reducing the increase in lactate caused by anaerobic glycolysis.[37] Insulin sensitivity decreases under stress, and effective analgesia can improve insulin resistance. High concentration of blood glucose can induce intracellular oxidative stress and mediate vascular endothelial injury, which is not conducive to the recovery of brain function, so it is important to maintain the stability of blood glucose in craniocerebral surgery. At present, there is no meta-analysis of the effect of SNB on stress response. Geze et al.[19] believed that SNB can inhibit the increase of plasma cortisol and ACTH during head nail placement. Huang et al.[42] believed that SNB combined with general anesthesia can effectively inhibit stress, and Abo-Zeid[43] also reported a similar outcome in Children.

Strength and Limitations

For our meta-analysis results, heterogeneity was high, and all results were analyzed with a random-effects model, however, this only balances statistical heterogeneity. The methodological quality of each study is different, and there are no clear restrictions on the types of craniotomy included. Different general anesthesia induction and maintenance drugs were included, irrespective of whether or not the drugs are given for prophylactic analgesia at the end of the operation, and the use of different pain scales to record pain scores. The measurement methods of blood pressure and heart rate (invasive or non-invasive blood pressure) and different types of local anesthetics are all potential factors causing heterogeneity. In our meta-analysis, the statistical results of 48-hour morphine consumption were unstable, and further clarification should be made by increasing the number of included studies in future studies. Our meta-analysis only reported angiotensin II, cortisol and blood glucose, while other hormones such as IL-6, IL-10, CPR, and endothelin were not reported because of a small number of studies, a concern that can be addressed in the future studies.

Implications for Practice

Irene Osborn[44] reviewed in 2010 that it is only necessary to block supraorbital nerve, supratrochlear nerve, zygomaticotemporal nerve, auriculotemporal nerve, greater occipital nerve, and lesser occipital nerve for scalp nerve block. A systematic review by Paul J. Zetlaoui in 2020[45] updated the nerves that need to be blocked for SNB, and identified seven nerves, namely the frontal (supraorbital and supratrochlear), zygomaticotemporal, and auriculotemporal nerves, the greater auricular nerve, the greater occipital nerve, the lesser occipital nerve, and the third nerve innervate the entire scalp. Usually, in one operation, not all of these seven nerves will be blocked. It is necessary to decide which ones to block according to the surgical incision marked by the surgeon. The supraorbital nerve and supratrochlear nerve are sensory nerves, originating from the eye branch of trigeminal nerve (V1), innervating the forehead and the upper eyelid. The zygomaticotemporal nerve originates from the maxillary branch (V2) of the trigeminal nerve and governs a small area of the outer canthus. The auriculotemporal nerve is a branch of the mandibular branch of the trigeminal nerve (V3) that governs preauricular and supra auricular sensations. The greater auricular nerve is a branch of the cervical plexus and innervates the posterolateral scalp and the periauricular skin. The greater occipital nerve arises from the posterior branch of C2 and ascends from the medial occipital artery through the posterior scalp. The lesser occipital nerve arises from the ventral branches of C2 and C3 and ascends from the back of the neck to innervate the scalp behind the ear. The third occipital nerve arises from the posterior rami of C3 and innervates the skin on the inside of the skull.

Implications for Research

At present, there is a lack of sufficient data to explain the effect of SNB on cognitive function and chronic headache, which can help to direct our next research work.

CONCLUSION

Scalp nerve block can effectively relieve the pain within 48 hours after craniotomy. The effect of preoperative block is better than that of postoperative block. The effect of ropivacaine and levobupivacaine is better than that of bupivacaine. Scalp nerve block may reduce morphine consumption in the first 48 hours after surgery, significantly prolong the time required for the first rescue analgesia after operation, effectively inhibit the stress response caused by surgical stimulation, stabilize hemodynamics, and reduce the incidence of postoperative nausea and vomiting.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

Xiaojing Wei and Zhongqiang Liu contributed equally.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the hospital's ethics committee. The patients have given their consent for publication. A copy of the written consent is available for review by the Editor of this journal.

AUTHOR DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

ACKNOWLEDGEMENT

Xiaojing Wei were major contributors in writing the manuscript. Zhongqiang Liu collected the patient data. Chong Liu and ShuKai Li performed both surgeries and followed up the patients. Jing An and Zhixue Wang realized the scarcity of the two cases, did literature searches, and revised the manuscript. All authors have read and approved the final manuscript.

FUNDING

This research received no external funding

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Appendix 1. PubMed search strategy

#1."craniotomy"[MeSH] Explode All Trees
#2."Decompressive Craniectomy"[MeSH]Explode All Trees
#3."Brain Neoplasms"[MeSH]Explode All Trees
#4."craniotomy"[Title/Abstract]
#5."craniectomy"[Title/Abstract]
#6.(brain)AND(surg* OR operat*)[Title/Abstract]
#7."post craniectom*"OR"post craniotomy*"[Title/Abstract]
#8."supratentorial AND surgery"[Title/Abstract]
#9."infratentorial AND surgery"[Title/Abstract]
#10.#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11."Anesthesia,Conduction"[MeSH]Explode All Trees
#12."Anesthesia,Local"[MeSH]Explode All Trees
#13."Anesthetics,Local"[MeSH]Explode All Trees
#14."Nerve Block"[MeSH]Explode All Trees
#15.(local*) OR (regional) [Title/Abstract]
#16.(analg*) OR (anesth*) OR (anaesth*)[Title/Abstract]
#17.#15 AND #16
#18.(pain) AND (perioperat* OR postoperat*)[Title/Abstract]
#19.nerve AND block*[Title/Abstract]
#20.#11 OR #12 OR #13 OR #14 OR #17 OR #18 OR #19
#21."scalp" Explode All Trees
#22.scalp*[Title/Abstract]
#23.#21 OR #22
#24.#20 AND #23
#25.(scalp*[Title/Abstract]) AND (block*[Title/Abstract])
#26."regional scalp block"[Title/Abstract] OR "SNB"[Title/Abstract] OR "RSB"[Title/Abstract]
#27.#24 OR #25 OR #26
#28.#10 AND #27
#29.#28 NOT awake[Title/Abstract]