A Comparison of Effects of Scalp Nerve Block and Local Anesthetic Infiltration on the Inflammatory Response, Hemodynamic Response, and Postoperative Pain in Patients undergoing Craniotomy for Cerebral Aneurysms: A Randomized Controlled Trial

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Abstract

BACKGROUND: The purpose of this study was to compare the effects of scalp nerve block (SNB) and local anesthetic infiltration (LA) with 0.75% ropivacaine on postoperative inflammatory response, intraoperative hemodynamic response, and postoperative pain control in patients undergoing craniotomy. METHODS: Fifty-seven patients were admitted for elective craniotomy for surgical clipping of a cerebral aneurysm. They were randomly divided into three groups: Group S (SNB with 15 mL of 0.75% ropivacaine), group I (LA with 15 mL of 0.75% ropivacaine) and group C (that only received routine intravenous analgesia). Pro-inflammatory cytokine levels in plasma for 72 hrs postoperatively, hemodynamic response to skin incision, and postoperative pain intensity were measured. RESULTS:The SNB with 0.75% ropivacaine not only decreased IL-6 levels in plasma 6 hrs after craniotomy but also decreased plasma CRP levels and increased plasma IL-10 levels 12 and 24 hrs after surgery compared to LA and routine analgesia. There were significant increases in mean arterial pressure 2 and 5 mins after the incision and during dura opening in Groups I and C compared with Group S. Group S had lower postoperative pain intensity, longer duration before the first dose of oxycodone, less consumption of oxycodone and lower incidence of PONV through 48 hrs postoperatively than Groups I and C. CONCLUSION: Preoperative SNB attenuated inflammatory response to craniotomy for cerebral aneurysms, blunted the hemodynamic response to scalp incision, and controlled postoperative pain better than LA or routine analgesia.

Background

Kenya ranks 10th out of 22 high TB burden countries globally[1]. The high prevalence of HIV in Kenya[1 2] is a major contributing factor to TB incidence. Siaya County in Western Kenya has a high burden of tuberculosis and HIV with a TB case notification rate of 400/100,000[3] and HIV prevalence of 15.1%[1].

Latent tuberculosis infection (LTBI) is the presence of *Mycobacterium tuberculosis* (MTB) in the body without signs and symptoms, or radiographic or bacteriologic evidence of tuberculosis (TB) disease[4]. One method to measure the trend of TB transmission is through repeated tuberculin surveys in order to estimate the trend of the prevalence of tuberculous infection and annual risk of tuberculous infection (ARTI). ARTI is used to measure the effectiveness of TB control programs. In addition, If TST conversion is a secondary endpoint for candidate vaccines preventing infection, ARTI estimates may also be used to inform the sample size of such trials.

Kenya has carried out several TST surveys to estimate the ARTI. These surveys were standardized by targeting primary school children aged 6-13 years and using the same TST technique [5-7]. The surveys were conducted in randomly selected districts and weighted for the underlying population distribution based on the most recent census. The ARTI estimates for Siaya district (where our present study was conducted) were 0.36%, 1.10% and 1.45% for the surveys conducted in 1986-1990, 1994-1996 and 2004-2007 respectively with a mean age of 10 years in each sampled population indicating a rising ARTI over time[5-7].

Bacillus Calmette-Guerin (BCG), the TB vaccine given at birth, has not been shown to reliably prevent pulmonary tuberculosis in adolescents8. Adolescents may be prime candidates to receive new more effective TB vaccines because they are entering an age of steeply rising TB rates 9. TB vaccine trials enrolling adolescents will need to measure efficacy using several endpoints, including TB disease incidence. Measuring the ARTI and the prevalence of infection in preparation for TB vaccine trials can give an indication of TB transmission in target communities. In this study, we aimed to estimate the annual risk of infection with MTB among 12–18 year olds. Some of the interim results of this study have previously been reported in an abstract at the Biennial infectious disease conference, Nairobi Hospital Convention Centre, Nairobi, Kenya, 2017.

Methods

Study design and sample size:

The study area, Karemo Division with a population of 85,000 people, part of Siaya County is under a continuous health and demographic surveillance system (HDSS)[10]. The HDSS collects biannual data using household surveys. In brief, the study area was divided into 17 clusters of approximately equal population size. The clusters were randomly selected to give each adolescent an equal probability of participation. Eight out of 17 clusters were used for enrolment. In each cluster, HDSS data was used to identify households with adolescents; parents at these households were then approached to have their children participate in the study. The survey was conducted as part of a study on TB prevalence and incidence which used a prospective observational cohort design enrolling adolescents aged 12-18 years[11].

Study Procedures

Informed Consent and clinical interviews

Parental consent was obtained at home by study staff prior to inviting adolescents to a mobile field site where minor assent was obtained prior to study participation. During enrolment, standard social demographic data were collected including age, gender, school enrolment status, parental social economic status, parental mortality, recent migration, and urban or rural residence. In addition, several clinical characteristics were collected including history of immunization with BCG, history of tuberculosis, BCG scar (we used the presence of a scar to stratify BCG status), weight and height. Study procedures have been described in more detail elsewhere[11]. The study received ethical approval of the Kenya Medical Research Institute and the US Centres for Disease Control and Prevention.

Tuberculin skin test and HIV testing:

All enrolled adolescents were offered a tuberculin skin test (TST) for LTBI after they provided a clinical history and vital signs were recorded. The TST used 0.1 ml of tuberculin purified protein derivative (PPD) containing 5TU (tuberculin units) RT23 with Tween 80 (Statens Serum Institute, Copenhagen, Denmark) and was injected intradermally into the middle dorsal region of the right forearm using a disposable tuberculin syringe and G.26 needle. Adolescents were offered a TST after giving clinical history and getting vital signs recorded. Adolescents returned after 72 hours for the reading of their TST results. Late TST readings were allowed up to a maximum of 7 days. All adolescents were offered HIV counselling and testing during the TST reading day. Parental/ guardian consent and adolescent assent were obtained prior to conducting HIV testing. Adolescents identified with HIV were referred to HIV care and treatment services at the Patient Support Centre at the Siaya District Hospital or to the nearest accessible Patient Support Centre.

The TST cut off we used as evidence for LTBI was ≥10mm in adolescents that did not have HIV or whose HIV status was unknown and ≥5mm in adolescents with HIV [12].

Statistical Analysis

Statistical analysis was performed using SAS 9.2 (SAS Institute Inc., Cary, NC, US). A three point moving average was used on the TST induration data to look for digit preference by observing differences in peaks between actual and smoothed data. The point prevalence of LTBI and 95% confidence intervals were calculated using survey procedures in SAS and adjusted for clustering. The prevalence of LTBI was estimated using the cut-off method and mirror method[13]. The cut-off method used the study defined cut-off of 10mm. In the mirror method, the mode of the distribution of those with presumed tuberculous infection is derived from the overall frequency distribution of TST reactions among the adolescents. Then, the total number of adolescents with positive TST reactions was estimated as the sum of the number of adolescents showing reaction sizes equal to the mode and double the number of adolescents with reaction sizes larger than the mode[13]. Bivariate analysis was used to determine significant associations between various risk factors and a positive tuberculin skin test. Factors significant at the p<0.2 level were further explored in a multivariate model using logistic regression. ARTI was calculated with the formula $ARTI=1-(1-\text{prevalence of infection})^{1/\text{mean age}}$[14]..

Results

A total of 5004 adolescents aged 12-18 years were enrolled between August 2008 and August 2009. All adolescents enrolled received tuberculin skin tests (TST) and a total of 4808 (96.0%) came for their TST readings and were included in the analysis. Of the 4808 with TST readings, the mean age was 14.4 (SD 1.9), 2327 (48%) were female, the mean body mass index (BMI) was 17.9 (SD 2.5), 4518 (94%) were currently enrolled in school, 4550 (95%) lived in a rural area, 1289 (26.8%) were orphaned, 861 (18%) had no BCG scar, 23(0.5%) were HIV positive, and 21(0.4%) gave a history of previous tuberculosis (table 1). There was no significant difference in the baseline characteristics between those who came back for TST readings and those that failed to turn up [data not shown].

TST indurations

Of the 4808 adolescents with TST results, 4166 (86.7%) were read within 4 days, 2762 (58%) did not have any induration. Of the 3947 adolescents with a BCG scar, 2177 (55%) no induration compared to 585/861 (86%) of adolescents without a BCG scar. Among adolescents with TST reactivity, the mean TST induration was 13.2 mm (SD 5.4). There was marked digit preference at 10 mm, 15 and 16 mm and some digit avoidance at 13 mm (Figure 1). The smoothed data (three-point moving average) of all the adolescents showed a mode of 17 (Figure 1). Smoothed data for adolescents with and without a BCG scar showed a mode of 17 and 18 respectively (Figure 1).

Prevalence of infection and ARTI

Using the cut-off method, including one adolescent with HIV with a TST of 5mm, the overall prevalence of LTBI was 1544/4808 (32.1%, 95% CI 29.2-35.1) with a corresponding ARTI of 2.6% (95% CI 2.2-3.1). Among adolescents with a BCG scar, the prevalence of positive reactions was 33.5% (95% CI 30.3-36.8) with an estimated ARTI of 2.7% (95% CI 2.2-3.2) and among adolescents without a BCG scar, the prevalence of positive reactions was 25.6% (95% CI 22.0-29.2) and the corresponding ARTI 2.1% (95% CI 1.1-3.1) (Table 2). The Mirror method suggested an ARTI of 2.2% (95% CI 1.7-2.7) in those with and 2.1% (95% CI 1.1-3.1) for those without a BCG scar.

Risk factors for Tuberculous Infection (LTBI)

Using the cut-off method, risk factors for a positive TST result were being male (OR 1.3, 95%CI 1.2,1.5), history of having a household TB contact (OR 1.5, 95%CI 1.2,1.8), having a BCG scar (OR 1.5,95%CI 1.2,1.7) living in a rural area (OR 1.4, 95%CI 1.1,1.9), and being out of school (OR 1.8, 95%CI 1.4,2.3). The mirror method identified being male (OR 1.4, 95% CI 1.2,1.7) and having a household TB contact (OR 1.6, 95%CI 1.2,2.1) as risk factors for a positive TST (Table 3).

All risk factors identified during bivariate analysis remained independently associated with a positive TST in multivariate analysis (Table 3).

Discussion

Our study showed an ARTI of 2.6% (95% CI 2.2-3.1) with the cut-off method and 2.2% (95% CI 1.8-2.6) with the mirror method, both of which are more than double the expected based on serial TST surveys among children aged 10 years in the same area that reported an ARTI of 1.1% [5-7]. This suggests that TB transmission may be more intense among adolescents than among young children. This is consistent with findings by Dodd et al who suggested estimates of TB infection based on surveys in children may underestimate infection incidence in adults[15]. A higher risk of infection among adolescents than among children of primary school age has also been reported elsewhere [16 17].

There are methodological challenges to measuring ARTI in adolescents, including the influence of previous BCG vaccination and exposure to environmental mycobacteria on TST results[18, 19]. Even though TST is a relatively inexpensive test, it has low specificity causing false positives in patients with history of BCG vaccination and environmental mycobacteria exposure[20]. In this study, BCG vaccination status was indeed associated with a positive TST result in the cut-off method, but the mirror method appeared to have eliminated this bias. ARTI was high both in those with and without a BCG scar, using either the cut-off or mirror method. Exposure to environmental mycobacteria appears not to have been a major factor given the low frequency of intermediate reactions (5-9 mm) and the similar prevalence estimate using the cut-off method and mirror method in those without BCG vaccination scar.

Risk factors for a positive TST were similar to those reported in studies elsewhere, including male sex[9] and having a BCG scar[21]. The higher risk of TB infection in males might be related to older boys having more contact with adult men among whom TB prevalence is higher, as suggested by Dodd[15]. Although only a small proportion (6%) of adolescents in this study were not currently enrolled in school, they were significantly more likely to have a positive TST compared to in school youth 45% and 31% respectively (OR 1.8, 95%CI 1.1, 2.9). However, this subgroup may be a good target population for intensified case finding and prevention. The majority of adolescents enrolled were of rural residence (94.6%) and this was associated with a positive TST also in a multivariate model. However, the difference was not large (32% versus 27%). As expected history of a household contact was strongly predictive of a positive TST 40.1% versus 31.4%). Previous TB surprisingly was not associated with a positive TST, but numbers were small. Having both parents deceased was associated with a positive TST (34% versus 31%)). The study area has a high HIV prevalence of 15.1%% [2] and many deaths among parents are likely to have been due to HIV/AIDS, which in this area is strongly associated with tuberculosis indicating a higher risk of LTBI in orphaned children before their parents died.

The ARTI estimates are derived from a point prevalence estimate and repeated TST surveys would need to be conducted to see how this correlates with the incidence of infection and age associated risks of infection[16, 17]. While BCG had some influence on TST reading results using the cut-off method, this was no longer the case using the mirror method. Digit preference was corrected by smoothing, though might be further reduced in the future by further strengthening training and supervision.

Preventing TB disease instead of infection has been the key goal of vaccine development [22]. Epidemiological and mathematical modelling studies have shown a pre-infection vaccine would have a high level impact on TB disease control[22]. A pre-infection vaccine will require choice of an age range where the risk of infection rises but before majority of the age group becomes infected. Adolescents are an important group for vaccination against TB because while TB incidence is relatively low in the age group 5-14 years, it rises rapidly in adolescence[23]. In our study majority of adolescents (67.9%) were TST negative indicating this would be a good age group to target for prevention of infection vaccine studies. We have reported on the incidence of tuberculosis in adolescents elsewhere[24]. The incidence of TB addresses the sample sizes needed for TB vaccine efficacy trials preventing disease; whether primary disease or reactivation from previous TB infection. Because of difficulties in having a human challenge model with tuberculosis a pathway to understanding the immune mechanisms of protection against tuberculosis with new vaccines would be to conduct prevention of infection with *M.tuberculosis* studies as a marker of biologic impact[22]. Since infection with *M.tuberculosis* happens much more often than TB disease, the trials will be much smaller and trial results would be obtained much sooner allowing a read-out on a TB vaccine candidate's likely efficacy before doing larger scale efficacy studies.

We conclude that the high TB transmission rates we found in this study, suggest that adolescents in this region may be an appropriate target group for TB vaccine trials including TB vaccine trials aiming to prevent infection.

Abbreviations

TB Tuberculosis

POI Prevention of infection

BCG Bacille Calmette-Guerin

TST Tuberculin skin test

HIV Human immunodeficiency virus

ARTI Annual Risk of tuberculous infection

LTBI Latent tuberculosis infection

MTB Mycobacterium tuberculosis

HDSS health and demographic surveillance system

PPD Purified protein derivative

TU Tuberculin units

Declarations

Ethics approval and consent to participate

The protocol and informed consent forms were reviewed and approved by the KEMRI local and national scientific steering committees and the KEMRI national ethical review committee and the Institutional Review Boards (IRBs) of CDC and the AERAS Global TB Vaccine Foundation. Parental consent was obtained at home by study staff prior to inviting adolescents to a mobile field site where minor assent was obtained prior to study participation

Consent for publication

Not applicable

Availability of data and material

The data supporting the findings of this study have been included as an additional supporting file in the submission.

Competing interests

KNCV tuberculosis foundation provided some funding for the project and participated in Manuscript preparation. The other funding agencies did not participate in data analysis or the preparation of this manuscript or in the decision to submit the manuscript for publication. The authors have no conflicts of interest relevant to this article to disclose.

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Authors' contributions

VN wrote the protocol, conducted the study, analysed and interpreted the data and wrote the manuscript. AB participated in data analysis and manuscript development. AH, EM, KL and MB participated in developing the protocol, reviewed data and multiple versions of the manuscript. All authors read and approved the final manuscript.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Tables

Table 1: Demographic characteristics of 4808 adolescents undergoing tuberculin skin testing in Kenya, 2008-2009.

Characteristic	Category	All (4808)
Tuberculin skin test (TST)	Reactive	1544 (32.1%)
	Non reactive	3264 (67.9%)
Gender	Female	2327 (48.4%)
	Male	2481 (51.6%)
School going	Yes	4518 (94.0%)
	No	290 (6.0%)
HIV status	Positive	23 (0.5%)
	Negative	1985 (41.3%)
	Unknown	2165 (45.0%)
Residence	Rural	4550 (94.6%)
	Urban	258 (5.4%%)
Previous TB	Yes	21 (0.4%)
	No	4787 (99.6%)
History of TB contact	Yes	138 (2.9%)
	No	4670 (97.1%)
Deceased parents	One parent deceased or both alive	3519 (73.2%)
	Both deceased	1289 (26.8%)
Socio economic status	Upper class	1582 (32.9%)
	Middle class	1636 (34.0%)
	Lower class	1590 (33.1%)

Table 2: ARTI estimates and prevalence of infection presented for all adolescents, those with and without a BCG scar

	N	Mean age (years)	≥10mm			*Mirror method 17 mm		
			P	ARTI	CI (95%)	P	ARTIπ	CI (95%)
All	4808	14.4	32.1%	2.6%	(2.2,3.1)	27.6%	2.2%	(1.8,2.6)
BCG scar	3947	14.4	33.5%	2.7%	(2.2,3.2)	27.8%	2.2%	(1.7,2.7)
BCG scar absent	859	14.2	25.6%	2.1%	(1.1,3.1)	27.0%	2.1 %	(1.1,3.1)

*The total number of adolescents with true reactions was calculated by adding the number of adolescents showing reaction sizes equal to the mode to double the number with reaction sizes larger than the mode to determine the numerator

The Cut-off for HIV+ was ≥5mm

π ARTI formula =1-(1-prevalence of infection) 1/mean age

CI 95% Confidence interval

Table 3: Risk factors for a positive tuberculin skin test (TST) for the 10mm cut-off method and the 17mm mirror method

Risk Factor		Tuberculin skin test >=10mm n=4808		Multivariate	Tuberculin skin test >=17mm n=4808				Multivariate
		Negative	Positive	OR, 95% CI	OR, 95% CI	Negative	Positive	OR, 95% CI	OR, 95% CI
Gender	Female	1650	677/2327 (29.1%)	1		2076	251/2327 (10.8%)	1	
	Male	1614	867/2481 (34.9%)	1.3(1.2,1.5)	1.3 (1.2,1.5)	2129	352/2481 (14.2%)	1.4 (1.2,1.6)	1.4 (1.2,1.7)
History of a house hold TB contact	Yes	224	150/374 (40.1%)	1.5 (1.2,1.8)	1.5(1.2,1.8)	119	19/138 (13.8%)	1	
	No	3040	1394/4434 (31.4%)	1		4086	584/4670 (12.5%)	1.6 (1.2,2.1)	1.6(1.2,2.1)
Previous TB	Yes	15	6/21 (28.6%)	1		18	3/21 (14.3%)	1	
	No	3232	1528/4787 (32.1%)	0.8 (0.3,2.1)		4163	597/4760 (12.5%)	1.2 (0.4,3.7)	
BCG Scar	Yes	2623	1324/3947 (33.5%)	1.3 (1.2,1.7)	1.5 (1.3,1.8)	3450	497/3947 (12.6%)	1.0 (0.8,1.3)	1.0 (0.8,1.3)
	No	641	220/861 (25.6%)	1		753	106/859 (12.3%)	1	
Residence	Urban	189	69/258 (26.7%)	1		231	27/258 (10.5%)	1	
	Rural	3075	1475/4550 (32.4%)	1.2 (1.0,1.5)	1.4 (1.1,1.9)	3974	576/4550 (12.7%)	1.2 (0.8,1.9)	1.2(0.8,1.9)
School going	Yes	3103	1415/4518 (31.3%)	1		3960	558/4518 (12.4%)	1	
	No	161	129/290 (44.5%)	1.8(1.4,2.2)	1.8 (1.4,2.3)	245	45/290 (15.5%)	1.3 (0.9,1.8)	1.3(1.0,1.8)
Orphaned	Yes	1136	585/1721 (34.0%)	1		1474	247/1721 (14.4%)	1	
	No	2128	959/3087 (31.1%)	1.1 (1.0,1.3)	1.1(1.0,1.3)	2731	356/3087 (11.5%)	1.3 (1.1,1.5)	1.3(1.1,1.5)

Figures

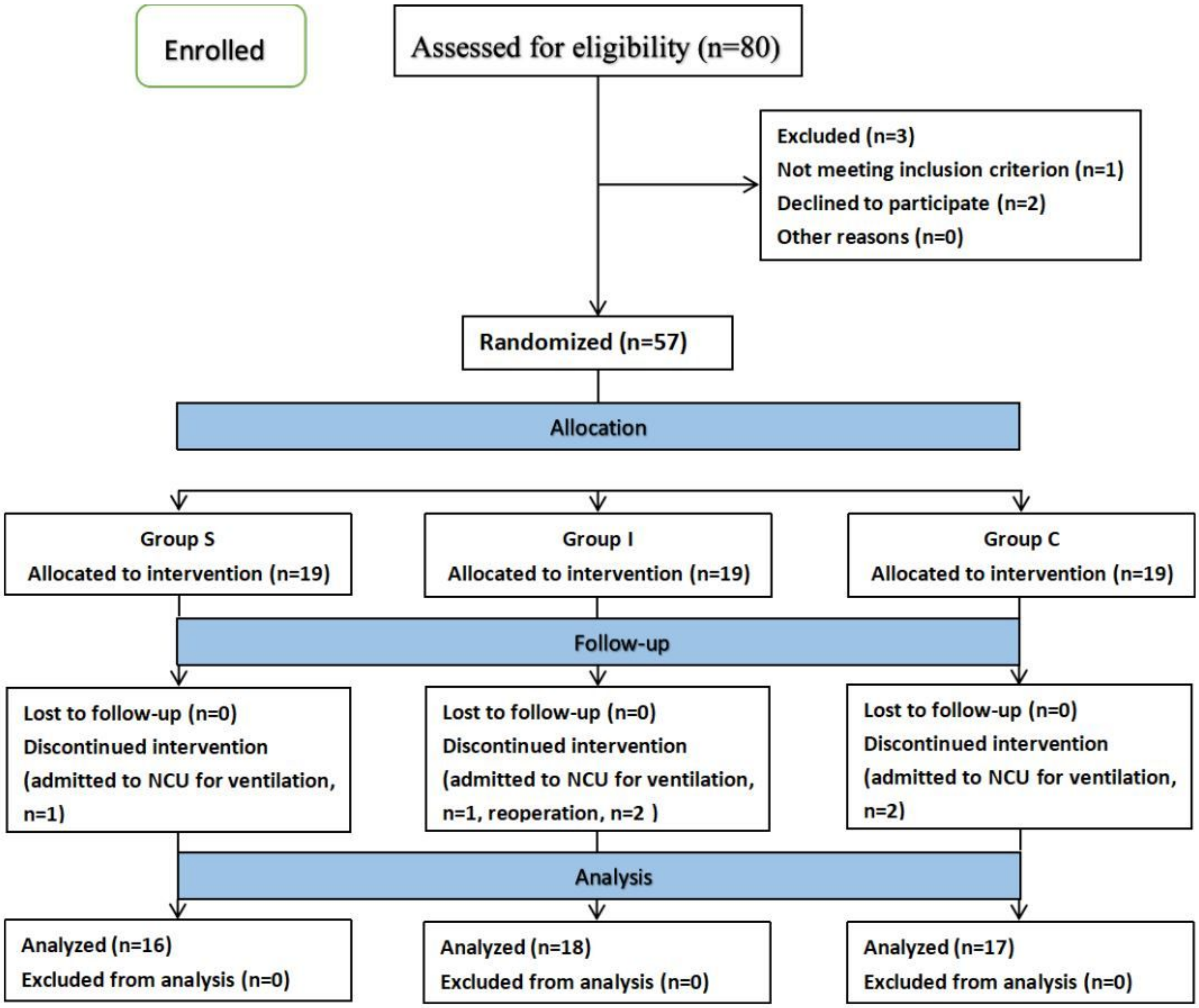

Figure 1

CONSORT flow diagram

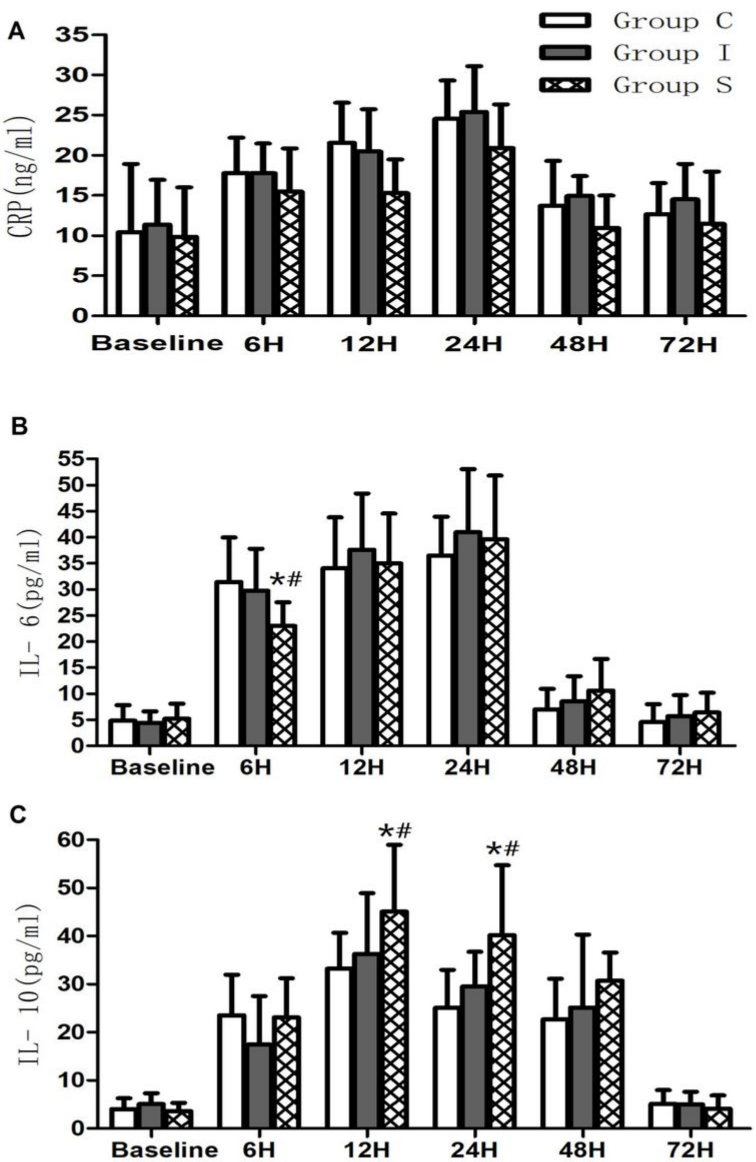

Figure 2

Concentrations of (A) C-reactive protein (CRP), (B) interleukin-6 (IL-6), and (C) interleukin-10 (IL-10) preoperatively (Pre-op) and 6, 12, 24, 48 and 72 hrs postoperatively in the three groups studied. Group C: control group, Group I: local anesthetic infiltration group, Group S: scalp nerve block group. *P<0.05, compared to Group C, #P<0.001, compared to Group I.

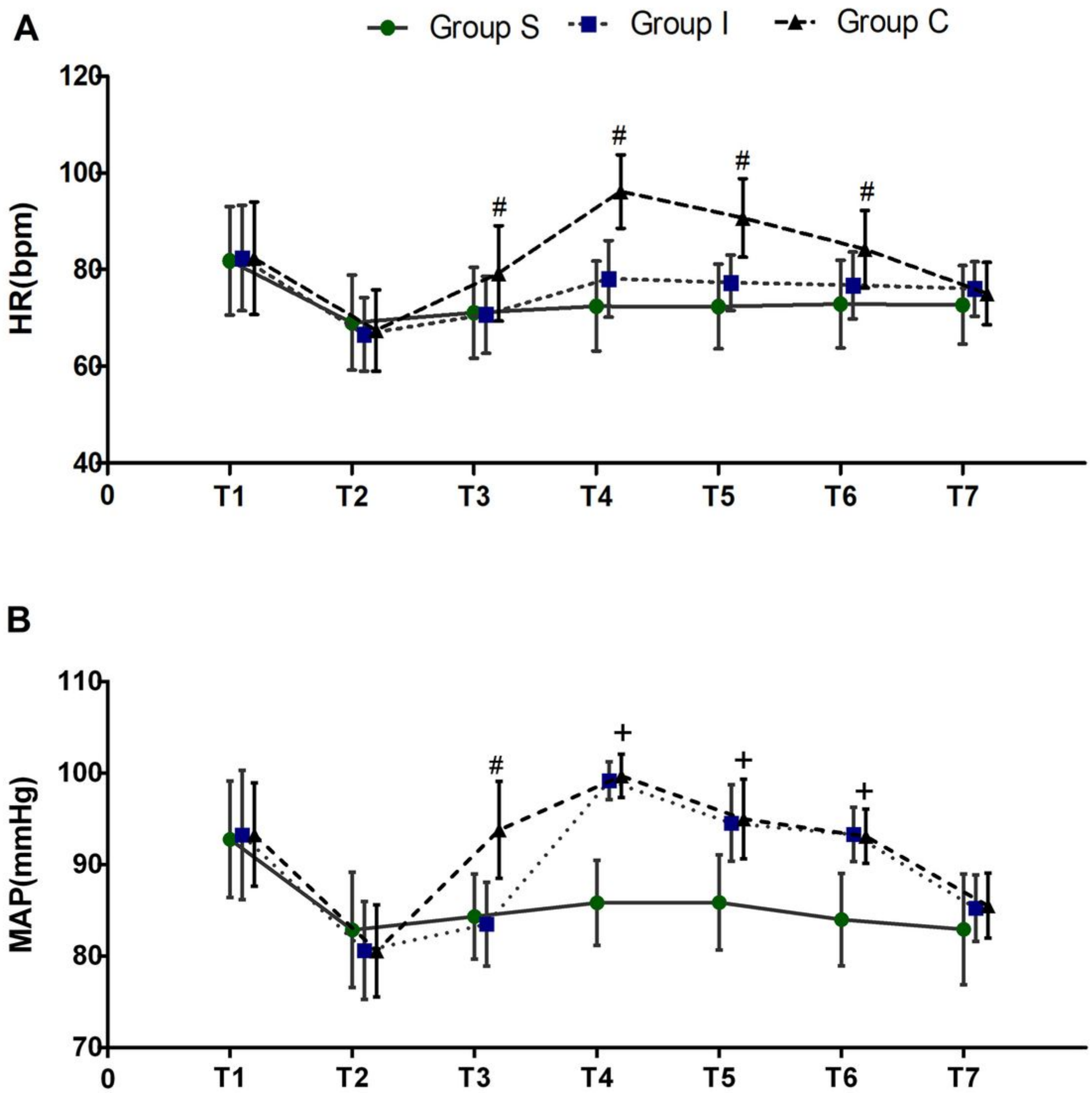

Figure 3

Comparison of HR and MAP changes during surgery. T1: before anaesthesia induction, T2: 5 mins after induction, T3: skin incision, T4: 2 mins after the incision, T5: 5 mins after the incision, T6: during dura opening, and T7: the end of the surgery. Group C: control group, Group I: local anesthesic infiltration group, Group S: scalp nerve block group. #P<0.05, for group C compared with group I and S, +P<0.001 for group I and C compared with group S.

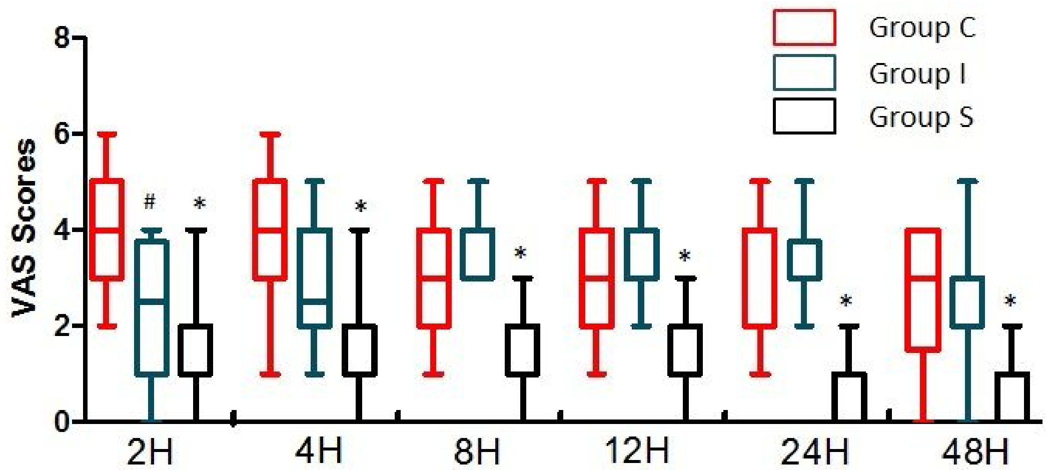

Figure 4

Comparison of VAS scores postoperatively for three groups. Group C: control group, Group I: local anesthesic infiltration group, Group S: scalp nerve block group. #P<0.05, Compared to group C, *P<0.001 for group S compared with group I and C.

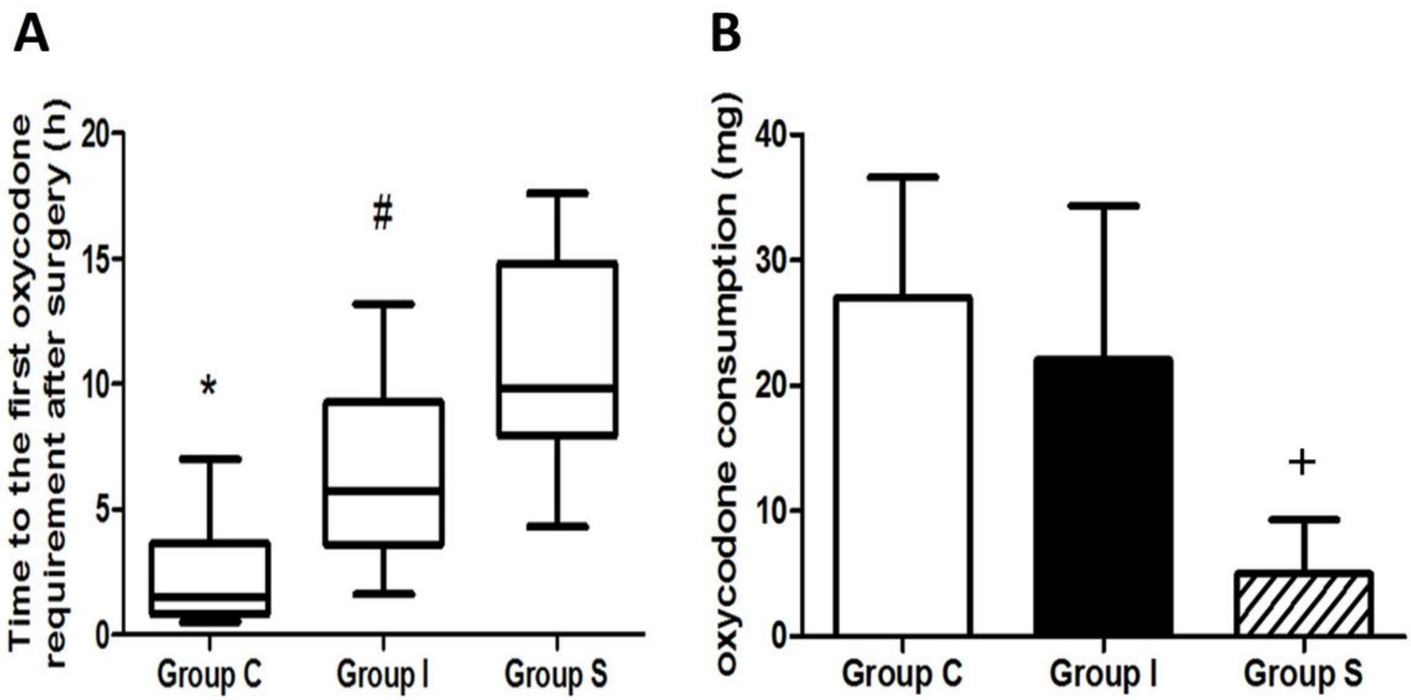

Figure 5

Comparison of (A) the first time patients requested rescue analgesia and (B) oxycodone consumption during the first 48 postoperative hrs. Group C: control group, Group I: local anesthesic infiltration group, Group S: scalp nerve block group. *P<0.01 for group C compared with group I and S, #P<0.05 for group I Compared with group S, +P<0.001 for group S Compared with group C and I.