

The Efficacy of Low-Dose Esketamine and Butorphanol in Treating Depression and Pain After Cesarean Section

Chunyan Zhao, Xiaofen Liu, Cibo Chen, Hongmei Yang, Bingchun Xia*

Dazhu County People's Hospital, Dazhou 635100, Sichuan Province, China

*Corresponding author: Bingchun Xia, xiabingchun6369@163.com

Copyright: © 2023 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

Abstract: *Objective:* To explore the efficacy of combining low-dose esketamine with butorphanol in treating depression and pain following cesarean section. *Methods:* 100 cases of elective cesarean section were selected and randomly assigned into two groups in a 1:1 ratio. All parturients who fulfilled the inclusion criteria received spinal anesthesia, maintaining the anesthesia level at T6. In the esketamine group, the dosage regimen comprised esketamine 0.5 mg/kg and butorphanol 10 mg, diluted with 0.9% sodium chloride injection to 100 mL. The control group received butorphanol 10 mg, diluted similarly. Analgesia in both groups commenced after cutting the umbilical cord, with a loading volume of 2 mL, a background infusion dose set to 2 mL/h, and patient-controlled analgesia at 2 mL with an effective interval time of 30 minutes. The main indicators included the maternal burnout scale (MBS) and numerical rating scale (NRS) for pain to assess postpartum depression and pain after surgery. *Results:* No significant differences were observed in MBS scores between the two groups on postoperative days 1 to 9 ($P > 0.05$). Postpartum depression was not detected in either group. Pain NRS scores at 24 and 48 hours after surgery, including incision and uterine contraction pain, showed no significant differences between the two groups ($P > 0.05$). Tramadol rescue was not administered to any patients in either group. Additionally, no adverse reactions requiring drug intervention occurred in either group. *Conclusion:* This study concluded that the combination of low-dose esketamine with butorphanol did not further optimize the analgesic effect of butorphanol but significantly improved postpartum depression after cesarean section. Further research is needed to investigate the impact of the ketamine postoperative analgesia regimen on postpartum analgesia and depression.

Keywords: Esketamine; Butorphanol; Depression and pain after cesarean section; Maternal burnout scale; Numerical pain rating scale

Online publication: December 26, 2023

1. Introduction

Cesarean section stands as a commonplace surgical procedure, constituting approximately one-third of all births in China ^[1]. Within the obstetrics department of Dazhu County People's Hospital, a staggering 90% of post-cesarean section mothers have exhibited a need for solid postoperative analgesia. Past research indicates that

roughly 75% of mothers encounter postpartum depression, typically peaking between 3 to 5 days post-delivery and persisting for days to weeks, which is an often-recognized precursor to postpartum depression [2]. Numerous studies underscore the close correlation between postpartum pain and negative mood [3], with cesarean section emerging as an independent risk factor for postpartum depression [4]. Additionally, initiation of cesarean section has been associated with disruptions to the immune system, bodily reactions, and stress responses, potentially leading to maternal psychological disorders [5]. Consequently, there is a compelling need to develop postoperative analgesia and antidepressant support tailored to cesarean section.

Esketamine, the dextrorotatory form of ketamine, primarily targets which still mainly acts on the N-methyl-D-aspartate (NMDA) receptor. It non-competitively inhibits glutamate-mediated activation of this receptor, exhibiting time- and frequency-dependent blockade, thereby reducing neuronal activity and imparting anesthetic and analgesic effects. Possessing double the hypnotic and analgesic potency of ketamine, esketamine induces fewer mental reactions. Furthermore, it exerts antidepressant effects through diverse mechanisms, including the promotion of synaptic protein synthesis and elevation of brain-derived neurotrophic factor, which is currently recognized as the antidepressant essence of esketamine [6]. Esketamine also sustains and repairs astrocyte structural integrity [7], and enhances inflammatory indicators through its influence on the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA)-cAMP-responsive element binding protein (CREB) signaling pathway [8], among other mechanisms, in the fight against depression.

Butorphanol, an opioid receptor agonist-antagonist, achieves analgesic effects by agonizing kappa receptors. A multi-center clinical study conducted by the obstetrics department of Dazhu County People's Hospital in 2018 demonstrated that butorphanol effectively manages pain post-cesarean section with minimal adverse reactions, obviating the need for concurrent use of antiemetics, such as 5-HT3 receptor antagonists. Consequently, the incidence of postoperative nausea, vomiting, and other side effects remains exceptionally low.

This study aims to investigate the efficacy of combining low-dose esketamine with butorphanol in addressing depression and pain following cesarean section. It is hypothesized that this combination can optimize analgesia, improving overall prognosis. It is anticipated to have a reduction in maternal depression symptoms after cesarean section, fostering a prompt postpartum recovery.

2. Materials and methods

2.1. General information

This study adopts a prospective, randomized, double-blind, placebo-controlled design and is conducted at a single center.

The subjects under investigation consist of women admitted to the obstetrics department of Dazhu County People's Hospital, who underwent cesarean section under spinal anesthesia between May 1, 2022, and February 28, 2023. Collected data encompassed maternal age, body mass index, previous childbirth history, education level, marital status, and pregnancy complications.

Inclusion criteria:

- (1) Age between 18 and 40 years.
- (2) ASA I–II level.
- (3) Gestational age between 37 and 42 weeks.
- (4) No contraindications for neuraxial anesthesia.
- (5) Voluntary signed informed consent and ability to cooperate throughout the study.

Exclusion criteria:

- (1) Allergic to any drugs or excipients used during anesthesia and postoperative analgesia.

- (2) Presence of severe obstetric complications or serious underlying diseases during pregnancy.
- (3) History of mental illness.
- (4) Dependence on drugs or alcohol.
- (5) Experience of current or past domestic violence.
- (6) Fetus diagnosed with congenital diseases.
- (7) Instances deemed unsuitable for inclusion in the study according to the researcher's judgment.
- (8) Urgent cesarean section.
- (9) Parturients experiencing failed neuraxial anesthesia puncture or yielding poor results requiring intravenous auxiliary medication or a switch to general anesthesia.
- (10) Critical emergencies, such as massive bleeding or amniotic fluid embolism during the operation, necessitate the need for rescue in seriously ill parturient women.

2.2. Anesthesia method

Following screening, parturient women meeting inclusion criteria but not falling under exclusion criteria underwent routine monitoring, including electrocardiogram (ECG), heart rate (HR), blood pressure (BP), and oxygen saturation (SpO₂) upon entering the operating room. Peripheral vein channels in both upper limbs were established, and compound sodium chloride injection was infused at a rate of 10 to 15 mL/kg/h. The mother assumed a left-sided lying position, holding her knees as much as possible. The midline approach of L3–4/L2–3 intervertebral space was chosen for puncture. Upon entering the subarachnoid space, cerebrospinal fluid was slowly withdrawn, followed by the addition of 1.5 mL of 0.75 % bupivacaine, diluted to 3 mL, and injected gradually. Subsequently, an epidural catheter was inserted 3 cm toward the head end. After the puncture, the mother assumed a supine position and a patented positioning pad was used to tilt 15° to 30° to the left, preventing supine hypotension syndrome. The operation commenced when the anesthesia level reached T6. Throughout the operation, 2% lidocaine was added to the epidural as needed. The infusion plan was adjusted based on blood pressure, with vasoactive drugs utilized to maintain hemodynamic stability.

2.3. Sample size

Stewart et al reported a postpartum depression incidence rate of 75% [9]. Domestic studies indicated rates ranging from 49% to 75. The combination of low-dose esketamine with sufentanil was found to reduce the incidence rate to 11%–42%. This study calculated the sample size based on an assumed incidence rate of 55 %, reducing to 25%. Considering a 20% loss to follow-up rate, 100 cases were included, with subjects allocated to the experimental and control groups in a 1:1 ratio.

2.4. Randomization and blinding

One hundred random numbers were generated using the random number table method. Serial numbers 1 to 50 were assigned to the esketamine group (EG), while serial numbers 51 to 100 were designated for the control group (CG). Throughout the trial, blinding measures were implemented for the parturients, follow-up personnel, anesthesiologists, and data analysts. The dispensing nurses were informed about the dosing plan.

2.5. Analgesic pump dosing scheme

Analgesia initiation occurred after cutting the umbilical cord. The parameters for the analgesic pump were as follows: loading volume of 2 mL, background infusion dose set at 2 mL/h, patient-controlled analgesia (PCA) at 2 mL, and a lock time of 30 min.

- (1) EG: Esketamine 0.5 mg/kg + butorphanol 10 mg, diluted with 0.9% sodium chloride injection to 100 mL.

- (2) CG: Butorphanol 10 mg, diluted to 100 mL with 0.9% sodium chloride injection (based on an analgesic program from a previously participated multi-center clinical study after cesarean section).

2.6. Observation indicators

Main indicators:

- (1) According to prior research, postpartum depression typically manifests within ten days after delivery. Accordingly, this research plan utilizes the maternal burnout scale (MBS) to assess maternal depression in each group on postoperative days 1, 3, 5, 7, and 9 following cesarean section. Postpartum depression is considered present if the total MBS score exceeds 8 points.
- (2) The numeric rating scale (NRS) of pain for both groups of mothers was recorded at 24 and 48 hours post-surgery. Additionally, the amount of tramadol used by mothers within 48 hours was documented to evaluate postoperative pain in both groups.

Safety indicators: The presence of maternal symptoms and signs such as vomiting, itching, hallucinations, headache, hypotension, or respiratory depression were documented at each observation point, followed by analyzing the occurrence of adverse reactions among the two groups of mothers.

2.7. Statistical analysis

Data statistics and analysis were conducted using R language and SPSS 22.0 software. For measurement data conforming to the normal distribution, the mean \pm standard deviation (SD) was employed, and the independent sample *t*-test was utilized for group comparison. If normal distribution criteria were not met, the rank sum test was applied. Enumeration data were expressed as *n* (%), with inter-group comparisons conducted using the χ^2 test or Fisher's exact test. Repeated measurement data underwent analysis of variance (ANOVA). A significance level of $P < 0.05$ denoted statistical differences.

3. Results

3.1. Basic characteristics of patients

A total of 132 cesarean-section patients were initially screened in this study. Ultimately, 96 women who completed follow-up were included for analysis, with 47 in the EG and 49 in the CG (**Figure 1**). No significant statistical differences were observed in general characteristics, pregnancy status, and obstetrical conditions between the two groups ($P > 0.05$; **Table 1**). The two groups exhibited no significant statistical differences in terms of past medical history, pregnancy complications, operation time, intraoperative use of vasoactive drugs, or intraoperative bleeding volume ($P > 0.05$; **Table 1**).

3.2. Comparison of MBS scores and postpartum depression between the two groups of mothers at each time point

MBS scores were assessed on the 1st, 3rd, 5th, 7th, and 9th days post-cesarean section. The results indicated no significant statistical difference in MBS scores between the two groups on postoperative days 1, 3, 5, 7, and 9 ($P > 0.05$). Furthermore, both groups demonstrated MBS scores below 8 points at each time point, indicating an absence of postpartum depression (**Table 2**).

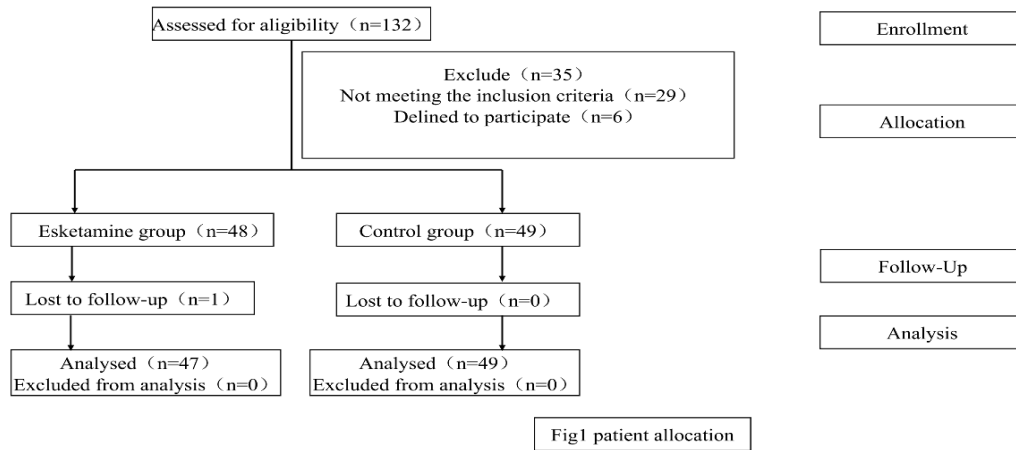


Figure 1. Patient allocation

Table 1. Characteristics, anesthesia, and procedure data

	EG	CG	P-value
Age, years	29.2 ± 4.8	29.7 ± 4.3	0.479
BMI	27.4 ± 3.0	27.9 ± 3.1	0.548
Education level			0.557
Middle school	6 (13%)	9 (18%)	
High school	18 (38%)	21 (43%)	
University	23 (49%)	19 (39%)	
Reproductive history	21 (45%)	25 (51%)	0.422
Pregnancy complications	6 (13%)	8 (16%)	0.774
Income level	8.5 ± 1.9	8.9 ± 2.3	0.365
Operative time	48.4 ± 15.5	45.9 ± 11.3	0.183
Intraoperative vasoactive drugs	29 (62%)	26 (53%)	0.417
Supine hypotensive syndrome	20 (43%)	22 (45%)	0.840
Intraoperative bleeding volume	574.4 ± 96.0	553.1 ± 88.8	0.376

Table 2. MBS scores at different time points after cesarean section (mean ± SD)

	1d	3d	5d	7d	9d
EG	1.3 ± 0.6	1.0 ± 0.3	0.8 ± 0.1	0.5 ± 0.2	0.2 ± 0.1
CG	2.0 ± 0.9	2.3 ± 0.6	1.6 ± 0.5	1.7 ± 0.7	1.2 ± 0.3
P-value	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

3.3. Pain scores and analgesia in the two groups within 48 hours after surgery

Table 3 shows that there was no significant statistical difference between the two groups in terms of uterine contraction pain or incision pain at 24- and 48-hours post-cesarean section ($P > 0.05$). **Table 4** shows that there was no statistical difference in the number of analgesics used within 24 hours ($P > 0.05$), and neither group required tramadol.

Table 3. NRS scores within 48 hours after cesarean section (mean ± SD)

	Contractive pain		Incision pain	
	24h	48h	24h	48h
EG	2.7 ± 1.4	1.9 ± 1.3	1.1 ± 0.9	0.8 ± 0.3
CG	2.9 ± 1.2	2.3 ± 1.4	1.6 ± 0.9	1.3 ± 0.5
<i>P</i> -value	> 0.05	> 0.05	> 0.05	> 0.05

Table 4. 24-hour analgesic and remedial medication (mean ± SD)

	EG	CG	<i>p</i> -value
Analgesics used (mL)	48.6 ± 6.8	56.2 ± 9.5	> 0.05
Remedial analgesia (%)	0	0	> 0.05

3.4. Adverse reactions of the two groups

No statistical differences were identified between the two groups in adverse reactions, such as abnormal mental behavior, nausea and vomiting, abnormal circulation, respiratory depression, and drowsiness ($P > 0.05$; **Table 5**).

Table 5. Comparison of adverse reactions [*n* (%)]

	EG	CG	<i>p</i> -value
Mental disorders	1 (2%)	0	> 0.05
Nausea and vomiting	3 (6%)	5 (10%)	> 0.05
Abnormal circulation	1 (2%)	2 (4%)	> 0.05
Respiratory depression	0	0	> 0.05
Drowsiness	0	2 (4%)	> 0.05

4. Discussion

This study revealed that the addition of 0.5 mg/kg esketamine to butorphanol, when compared with the use of butorphanol alone, did not lead to further optimization of butorphanol's analgesic effects. However, it did demonstrate efficacy in pain relief and improvement of postpartum depression. Notably, no significant instances of postpartum depression were observed, whether the combination of the two medications was administered or butorphanol alone, following cesarean section. Importantly, both medication regimens achieved robust analgesic effects without the need for tramadol or other supplementary analgesic drugs. Additionally, neither severe adverse reactions nor adverse reactions necessitating drug intervention were identified in either group. It is worth noting that, to date, there are no existing clinical studies investigating the impact of combining esketamine with butorphanol on pain and depression following cesarean section.

In a randomized controlled study conducted by Wang *et al.* [10], 240 pregnant women were included in a 1:1:1:1 ratio to explore the impact of different doses of esketamine combined with sufentanil on postoperative analgesia and postpartum depression. The study revealed that when administered separately at doses of 0.1 mg/kg, 0.2 mg/kg, and 0.4 mg/kg, either in combination with sufentanil or alone, the concurrent use of esketamine significantly reduced postoperative sufentanil consumption and enhanced postoperative anesthesia. This not only minimized the incidence of postpartum depression at 1 week and 6 weeks after surgery but also lowered the occurrence of postoperative nausea and vomiting.

Furthermore, three other studies corroborated these findings, highlighting that the combined medication group exhibited a lower incidence of postpartum depression and reduced opioid consumption compared to sufentanil alone ^[11-13]. A retrospective cohort study provided further support, confirming that the NRS pain score for sufentanil combined with esketamine was notably lower than that for esketamine alone ^[14]. Maternal sleep quality showed significant improvement within one week, and both recovery rate and quality at three months post-surgery were notably enhanced.

Dexmedetomidine, an alpha-2 receptor agonist, operates by inhibiting the release of excitatory neurotransmitters, such as catecholamines, through the activation of alpha-2 receptors. This mechanism results in central sedative and anxiolytic effects ^[15]. Earlier studies highlighted that different doses of dexmedetomidine combined with butorphanol post-cesarean section could enhance sustained analgesia ^[16,17]. Notably, higher doses exhibited superior analgesic outcomes without significant changes in sedation effects. However, the combined impact on postpartum depression remains unexplored.

In a prior multi-center clinical study on varied butorphanol doses for postoperative analgesia, the findings suggested that the use of 8 mg and 12 mg, diluted with 0.9% sodium chloride to 100 mL, resulted in low VAS scores, particularly for uterine pain, and reduced incidence of nausea and vomiting, even without antiemetic drug use. Although statistically significant improvements were not observed in the current study, the combined medication group exhibited varying reductions in MBS and NRS scores, especially incision pain, with no severe adverse reactions. Consequently, further research is warranted to explore the efficacy of esketamine combined with opioid receptor agonist-antagonists in post-cesarean analgesia and postpartum depression.

Limitations of this study include its single-center nature, restricted to the county's population. Further endeavors should involve multi-center clinical studies to enhance population representativeness. Additionally, the short follow-up time for postpartum depression necessitates further evaluation of long-term outcomes. The assessment scale's relative singularity in this study may pose a risk of missed diagnoses, emphasizing the importance of comprehensive evaluations through multiple dimensions in subsequent research.

5. Conclusion

This study revealed that the addition of low-dose esketamine to butorphanol did not enhance the analgesic effect of butorphanol further. Surprisingly, it improved postpartum depression following cesarean section. However, it is noteworthy that the incidence of postpartum depression in both medication regimens was notably lower than what has been reported in previous studies. The implications of a postoperative analgesic regimen combining opioid receptor agonist-antagonists with esketamine on postpartum analgesia and postpartum depression necessitate further investigation.

Disclosure statement

The authors declare no conflict of interest.

References

- [1] Qiao J, Wang Y, Li X, et al., 2021, A Lancet Commission on 70 Years of Women's Reproductive, Maternal, Newborn, Child, and Adolescent Health in China. *Lancet*, 397(10293): 2497–2536. [https://doi.org/10.1016/S0140-6736\(20\)32708-2](https://doi.org/10.1016/S0140-6736(20)32708-2)
- [2] Zanardo V, Volpe F, de Luca F, et al., 2020, Maternity Blues: A Risk Factor for Anhedonia, Anxiety, and Depression

Components of Edinburgh Postnatal Depression Scale. *J Matern Fetal Neonatal Med*, 33(23): 3962–3968. <https://doi.org/10.1080/14767058.2019.1593363>

- [3] Gastaldon C, Solmi M, Correll CU, et al., 2022, Risk Factors of Postpartum Depression and Depressive Symptoms: Umbrella Review of Current Evidence from Systematic Reviews and Meta-Analyses of Observational Studies. *Br J Psychiatry*, 221(4): 591–602. <https://doi.org/10.1192/bjp.2021.222>
- [4] Zhao X-H, Zhang Z-H, 2020, Risk Factors for Postpartum Depression: An Evidence-Based Systematic Review of Systematic Reviews and Meta-Analyses. *Asian J Psychiatr*, 53: 102353. <https://doi.org/10.1016/j.ajp.2020.102353>
- [5] Dutsch-Wicherek MM, Lewandowska A, Zgliczynska M, et al., 2020, Psychiatric Disorders and Changes in Immune Response in Labor and Postpartum. *Front Biosci (Landmark Ed)*, 25(8): 1433–1461. <https://doi.org/10.2741/4863>
- [6] Al-Harbi KS, 2012, Treatment-Resistant Depression: Therapeutic Trends, Challenges, and Future Directions. *Patient Prefer Adherence*, 6: 369–388. <https://doi.org/10.2147/PPA.S29716>
- [7] Ardalan M, Rafati AH, Nyengaard JR, et al., 2017, Rapid Antidepressant Effect of Ketamine Correlates with Astroglial Plasticity in the Hippocampus. *Br J Pharmacol*, 174(6): 483–492. <https://doi.org/10.1111/bph.13714>
- [8] Réus GZ, Abaleira HM, Titus SE, et al., 2016, Effects of Ketamine Administration on the Phosphorylation Levels of CREB and TrkB and on Oxidative Damage After Infusion of MEK Inhibitor. *Pharmacol Rep*, 68(1): 177–184. <https://doi.org/10.1016/j.pharep.2015.08.010>
- [9] Stewart DE, Vigod S, 2016, Postpartum Depression. *N Engl J Med*, 375(22): 2177–2186. <https://doi.org/10.1056/NEJMcp1607649>
- [10] Wang W, Xu H, Ling B, et al., 2022, Effects of Esketamine on Analgesia and Postpartum Depression After Cesarean Section: A Randomized, Double-Blinded Controlled Trial. *Medicine (Baltimore)*, 101(47): e32010. <https://doi.org/10.1097/MD.00000000000032010>
- [11] Yang SQ, Zhou YY, Yang ST, et al., 2023, Effects of Different Doses of Esketamine Intervention on Postpartum Depressive Symptoms in Cesarean Section Women: A Randomized, Double-Blind, Controlled Clinical Study. *J Affect Disord*, 339: 333–341. <https://doi.org/10.1016/j.jad.2023.07.007>
- [12] Lou F, Wang C, Dong X, et al., 2023, Analysis of the Analgesic Effect, Emotion, and Safety of Esketamine in Cesarean Section Analgesia for Puerperae. *Altern Ther Health Med*, 29(7): 424–428.
- [13] Liu Q-R, Zong Q-K, Ding L-L, et al., 2023, Effects of Perioperative Use of Esketamine on Postpartum Depression Risk in Patients Undergoing Cesarean Section: A Randomized Controlled Trial. *J Affect Disord*, 339: 815–822. <https://doi.org/10.1016/j.jad.2023.07.103>
- [14] Wang Y, Zhang Q, Dai X, et al., 2022, Effect of Low-Dose Esketamine on Pain Control and Postpartum Depression After Cesarean Section: A Retrospective Cohort Study. *Ann Palliat Med*, 11(1): 45–57. <https://doi.org/10.21037/apm-21-3343>
- [15] Afonso J, Reis F, 2012, Dexmedetomidine: Current Role in Anesthesia and Intensive Care. *Rev Bras Anesthesiol*, 62(1): 118–133. [https://doi.org/10.1016/S0034-7094\(12\)70110-1](https://doi.org/10.1016/S0034-7094(12)70110-1)
- [16] Liu H, Wang Y, Li F, et al., 2022, Analgesic and Sedative Effects of Different Doses of Dexmedetomidine Combined with Butorphanol in Continuous Analgesia after a Cesarean Section. *Front Surg*, 9: 896536. <https://doi.org/10.3389/fsurg.2022.896536>
- [17] Liu S, Peng P, Hu Y, et al., 2021, The Effectiveness and Safety of Intravenous Dexmedetomidine of Different Concentrations Combined with Butorphanol for Post-Caesarean Section Analgesia: A Randomized Controlled Trial. *Drug Des Devel Ther*, 15: 689–698. <https://doi.org/10.2147/DDDT.S287512>

Publisher's note

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.