A comparative study on the analgesic efficacy, progress and outcome of labour using epidural versus combined spinal epidural analgesia in labour

Dr Haneen Abdul Raoof, Dr Elizabeth Joseph

Abstract— **BACKGROUND**:This article aims to examine the analgesic efficacy, progression, and outcome of CSE (combined spinal-epidural) and epidural analgesia in labour.**MATERIALS & METHODS**:The Department of Anaesthesiology at Government Medical College, Thrissur undertook this prospective observational research in association with the Department of Obstetrics and Gynaecology, for a period of 18 months from January 2018 to June 2019 among parturients admitted to the labour room, for safe confinement. Sixty parturients in established labour and requesting epidural were alternatively divided into two groups. Group Epidural received a bolus of 10 ml 0.2% ropivacaine with 2 mcg/ml fentanyl as 5 ml increments 5 mins apart. Group CSE received a bolus of 1 ml of 0.2% ropivacaine and 0.5 ml 25 mcg of fentanyl in the intrathecal space (1.5 ml total). Both groups were started on continuous infusion with 0.1% ropivacaine with 2 mcg/ml fentanyl. Analgesic efficacy, maternal haemodynamics, fetal heart rate, progress of labour(time from initiation of analgesia to delivery), level of sensory and motor blockade, incidence of caesarian section or instrumental delivery and occurrence of side effects were recorded using a clinical performa.**RESULTS:**In the CSE group compared to the Epidural group, the Numeric Rating Scale(NRS) for pain following analgesia administration was considerably lower. The duration of labour was much longer in the group receiving an epidural than in the CSE group. The CSE group had a shorter second stage of labour. The requirement of top-up boluses was lesser for group CSE. The maternal pulse rate and blood pressure changes in the initial 5,10,and 15 mins after administration of CSE were more compared to the Epidural group. The sensory level obtained upon instituting CSE analgesia was statistically significant indicating that sensory blockade of T6 and T8 was common with CSE as opposed to T8 and T10 in the Epidural group. None of the parturients had any motor blockade. The outcome of labour was comparable in either group irrespective of the technique of analgesia. The incidences of post-procedure complications like maternal hypotension & bradycardia, foetal bradycardia, and pruritus were none. **CONCLUSION**:Similar extent of pain reduction were given by CSE and epidural analgesia. The quality of analgesia was better with CSE. The progress of labour was shorter with CSE. The outcome of labour was comparable in either group. The change in hemodynamic parameters during the initial period could be due to better pain relief with CSE.

Index Terms: Epidural, Combined Spinal Epidural, Ropivacaine, Fentanyl, Labour Analgesia.

1 Introduction

Parenteral opioids, nitrous oxide, and non-pharmacologic interventions have been outperformed by neuraxial analgesia in terms of the quality of labour, with little impact on the method of delivery and maternal and neonatal outcomes. Regional analgesia treatments enhance foetal oxygenation and placental perfusion while reducing the depressive effects of sedatives and opioids on the foetus. Epidural analgesia is a popular technique. The CSE approach for labour analgesia, on the other hand, has gained significant popularity[1].There has been a lot of disagreement over whether the increased use of neuraxial analgesia during labour has had an impact on the rising incidence of caesarean delivery.

2 Objectives

Our primary objectives were to compare epidural and CSE analgesia in labour with regard to analgesic efficacy, the progress of labour, outcome of labour. Our secondary objectives were to assess the highest sensory blockade level attained, the intensity of motor blockade, and the hemodynamic variations, patient satisfaction score and side effects.

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3 MATERIALS & METHODS

The Department of Anaesthesiology at Government Medical College, Thrissur undertook this prospective observational research in association with the Department of Obstetrics and Gynaecology, for a period of 18 months from January 2018 to June 2019 among parturients admitted to the labour room, for safe confinement, after obtaining clearance from Institutional Ethical Committee.

3.1 Sample Size

A total of 60 parturients were alternatively divided into two groups of 30 each. The following formula was used to determine the sample size; n= [(Zα+Zβ) x SD] 2 / d2 in each group, where Zα+Zβ = 7.8; SD=0.6; d=0.3; which were calculated from previous studies
The SD and d were calculated from a study conducted by David L Hepner and Robert R Geisser at Brigham and Women's Hospital[2].

3.2 Inclusion Criteria

Uncomplicated pregnancy with no cephalopelvic disproportion
Gestational age ≥36 weeks
Normal foetus in vertex presentation
Parturients in spontaneous and induced labour
Parturients who gave consent

3.3 Exclusion Criteria

Parturient refusal
Preterm gestation
Parturients with coagulopathy
Parturients with infection at the injection site
Patients in septicaemia
Parturients with active maternal haemorrhage and hypovolemia

3.4 Statistical Analysis

Results for continuous data in the current investigation were presented as range values, and Mean±Standard Deviation. Categorical data were presented as numbers and percentages for the independent t-test for comparing the two groups, and the chi-square test was utilized to examine group differences. For statistical significance, a P-value of 0.05 or less was utilized. SPSS was the software used for analysis.

4 RESULTS

4.1 Demographic Distribution

The study's sample population ranged in age from 19 years to 35 years old. When the groups were examined using an independent t-test, there was no statistically considerable difference between the groups (P = 0.71).
The minimum weight in the study population was 45kg, and the maximum weight was 86 kg. The weight difference between the groups is not significant statistically. Independent t-test was done and the P-value = 0.50. The maximum number of parturients belonged to the group 60-69 kg.

Using an independent t-test, the baseline cervical dilatation between the groups revealed that there was no significant difference between the groups in terms of cervical dilatation (P=0.42).

4.2 Analgesic Efficacy

Scores were comparable before the initiation of analgesia (P = 0.36). Using an independent t-test, the examination of NRS during analgesia revealed lower ratings for those who were administered CSE compared to epidural analgesia (P-value <0.001). Fig 1.

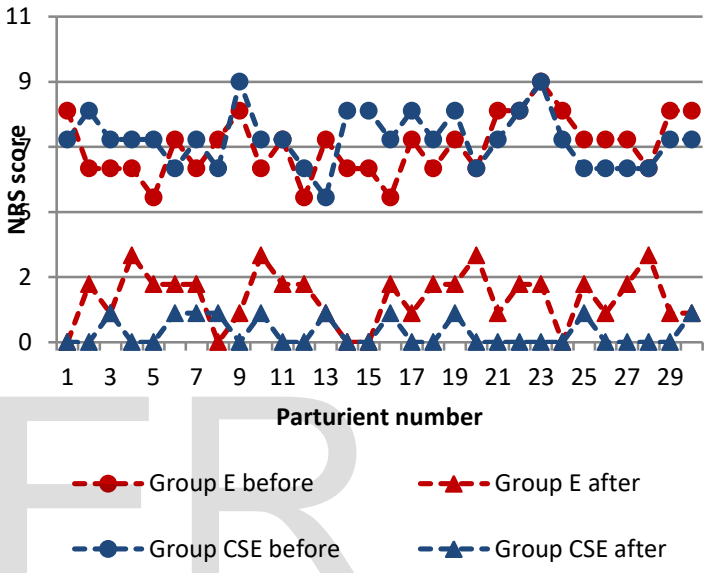

Fig 1: Comparison of numeric rating scale

4.3 Requirement of Top up Boluses

When utilising an independent t-test, it was statistically significant that parturients who were administered epidural analgesia required fewer top-up boluses than those who were administered CSE analgesia (P-value=0.001).

4.4 Progress of Labour

Table 1: Comparison of Progress of Labour

	Group Epidural	Group CSE	*P* value
Time from analgesia initiation to full cervical dilatation	6.000 ± 2.26	4.550 ± 1.71	**0.007**
Duration of 2nd stage	1.375 ±.76	1.03 ±.53	**0.049**

The independent t-test comparison between the two groups revealed a substantial statistical difference in terms of labour progress. The Epidural group of parturients took a longer time

to progress in labour. This was assessed in terms of time from analgesia initiation to full cervical dilatation and 2nd stage length of labour.

4.5 Outcome of Labour

The analysis of the outcome of labour between the 2 groups showed that normal delivery was the main outcome of labour followed by instrumental delivery and the lowest for caesarean section. No statistical significance was indicated by a chi-square value of 0.610 and a P-value of 0.7.

4.6 Comparison of Sensory Blockade between the Groups

Using the chi-square test, the sensory blockade between the two groups was compared, and the P-value was 0.001; T6, T8, were significantly more prevalent in parturients who were administered CSE analgesia than in those who received epidural analgesia. There were a few cases with higher levels (up to T4) with the CSE technique. Fig 2.

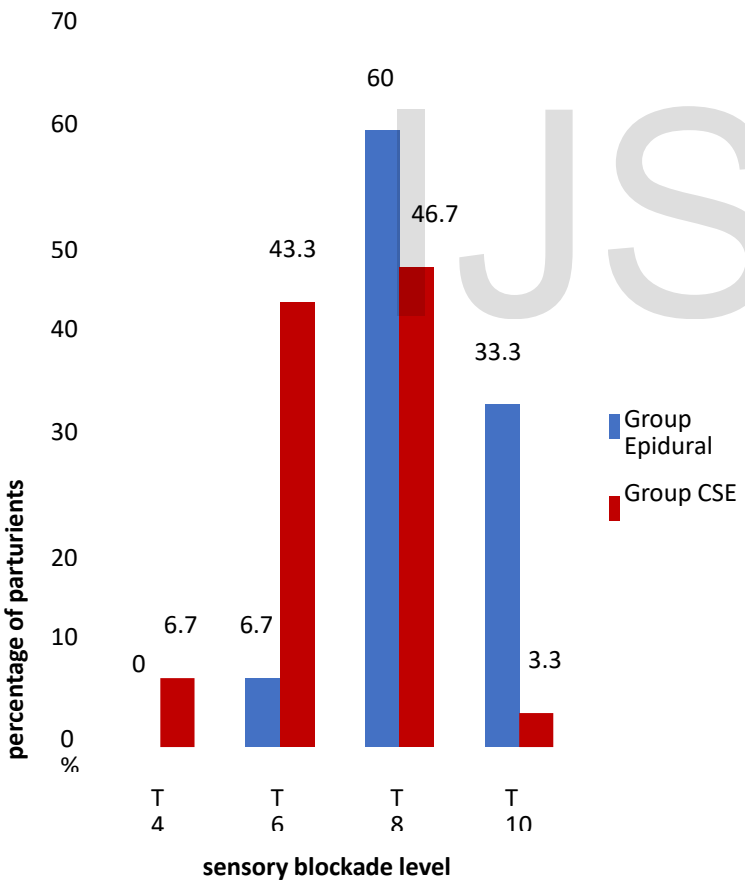

Fig 2: Comparison of sensory blockade

4.7 Comparison of Motor Blockade

None of the parturients belonging to either group developed motor blockade.

4.8 Comparison of Maternal Haemodynamics

Table 2:. Comparison of Maternal Haemodynamics

Time Intervals (mins)	Group Epidural	Group CSE	*P* Value
1	88.13 ± 9.27	81.57 ± 7.47	**0.004**
5	86.97 ± 8.23	81.57 ± 8.22	**0.01**
15	84.07 ± 9.18	79.93 ± 6.54	**0.05**
30	80.07 ± 9.64	80.07 ± 7.28	1.00
60	80.70 ± 8.44	80.07 ± 7.28	0.62
90	79.77 ± 9.76	79.03 ± 6.64	0.73
120	81.17 ± 10.16	80.23 ± 7.62	0.68
180	82.53 ± 8.09	78.5 ± 6.35	**0.03**
Comparison of Pulse Rate Variations			
Time Intervals (mins)	**Group Epidural**	**Group CSE**	***P* Value**
1	116.67 ± 14.09	108.13 ± 9.79	**0.009**
5	112.80 ± 12.79	103.33 ± 8.934	**0.002**
15	112.20 ± 12.84	102.57 ± 8.75	**0.001**
30	110.40 ± 10.20	104.73 ± 5.45	**0.01**
60	110.83 ± 11.86	107.60 ± 6.26	0.19
90	109.20 ± 11.44	110.50 ± 4.96	0.57
120	111.67 ± 11.32	110.83 ± 6.17	0.72
180	114.37 ± 9.65	110.30 ± 7.05	0.06
Comparison of Systolic BP Variations			
Time Interval (mins)	**Group Epidural**	**Group CSE**	***P* Value**
1	77.30 ± 9.93	69.07 ± 7.31	**0.001**
5	75.27 ± 9.32	69.03 ± 6.66	**0.004**
15	75.33 ± 7.43	68.37 ± 6.44	**<0.001**
30	73.27 ± 7.58	69.40 ± 6.30	**0.03**
60	73.30 ± 8.00	69.80 ± 7.60	0.08
90	73.10 ± 8.20	69.30 ± 6.01	**0.04**
120	71.70 ± 5.60	68.83 ± 5.77	O.06
180	71.83 ± 7.24	69.23 ± 6.19	0.14
Comparison of Diastolic BP Variations			

Pulse rate variations
CSE analgesia was associated with a lower heart rate at time intervals of 1,5,15 and 180 mins in comparison to epidural analgesia. On an independent t-test, this association was significant statistically with P-values <0.05.
Systolic BP variations
Compared to the parturients who got epidural analgesia, the decline in systolic blood pressure was more pronounced in those who received CSE analgesia. An independent t-test that produced a P-value that was primarily <0.05 made this obvious at time intervals of 0,1,5,15,30 mins.
c. Diastolic BP variations
The drop in diastolic BP was more obvious with parturients who received CSE analgesia, especially in the time intervals of 1, 5, 15, 30 and 90 mins compared to epidural analgesia. This association was statistically significant in the 2 groups upon doing an independent t-test which gave a P-value of <0.05.

4.9 Comparison of Satisfaction Scores

Parturients who received CSE analgesia had better satisfaction scores compared to those who received epidural analgesia. This correlation was significant statistically with a P-value of 0.001 and a chi-square value of 10.82.Fig 3.

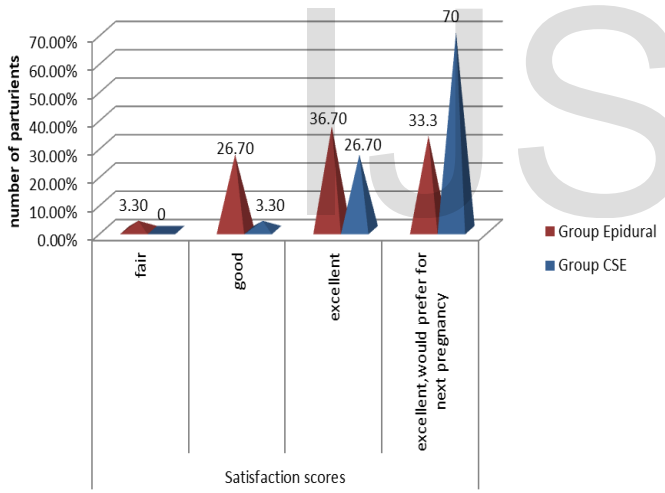

Figure 3: Comparison of satisfaction scores

Prevalence of Side effects

Table 3. Comparison of Incidence of Side-Effects

Side Effects	Number of Parturients	
	Group Epidural	Group CSE
Maternal Hypotension &Bradycardia	0	0
Foetal Bradycardia	0	0
Pruritus	0	0

Adverse effects like maternal hypotension & bradycardia, foetal bradycardia and pruritus were not seen in parturients who received either type of analgesia.

5 DISCUSSION

Age differences between the groups were comparable. In this research, the oldest parturient was 35 years old, and the youngest was 19. The maximum number of parturients fell into the age group of fewer than 26 years. This is a reflection of the social and cultural norm of getting married in the early twenties in our society. The number of caesarean sections and assisted deliveries was minimal in our study. This may also be attributed to the age groups of our parturients. Ecker et al found an incidence of increased caesarean section and advanced maternal age in parturients[3].
Labour analgesia was instituted upon maternal request irrespective of the cervical dilatation. Maximum parturients in our study had cervical dilatations of 3cm and 4cm at the initiation of analgesia. This may be explained by the obstetric practices in our institution. Cervical dilatations of both groups were also comparable. In a randomised study including 750 expectant mothers, Wong et al. discovered that giving neuraxial analgesia early in labour (when the cervical dilatation was less than 4cm) didn't increase the incidence of caesarean birth[4].
The progress of labour in my study was assessed using two parameters. i.e.,time from initiation of analgesia up to complete cervical dilatation and the time for 2ndstage of delivery. While comparing the time from analgesia initiation to full cervical dilatation the parturients in group epidural took around 6 hrs as opposed to group CSE which took around 4.5hr only. The labour duration of the 2ndstage was around 1hr 37mins for group Epidural as opposed to 1hr 3 mins for group CSE. While multiparous women progressed with a minimum cervical dilatation rate of 1.5cm/hr, nulliparous women's cervical dilatation rate was about 1.2cm/hr. In our study, the primi to multigravidae ratio was the same in either group hence this could not have contributed to the labour prolongation in group Epidural. In either group, the duration of stages of labour conforms to the standard duration expected for any par-

turient. In their research, ZakiM et al.[5] discovered that nulliparous women under the age of 20 had the slowest progress in labour, taking the longest to progress from 4 to 10cm of cervical dilatation. In our study, group epidural had more parturients of age less than 22 yrs which could have contributed to the same. Age increased the rate at which multiparous women progressed through labour.

In a study by Zaki M. et al., it was shown that the length of 2ndstage of labour, both with and without an epidural, rose directly with age (P<0.001), and that, across all age groups, the use of an epidural was linked to a rise in 2ndstage duration of around 0.4 hours. Similar to other studies, ours found that the 2ndstage was longer in the Epidural group than in the CSE group by around 0.34hr, which was statistically significant. Tsen et al. in their study on hundred nulliparous parturients found that those who received CSE analgesia progressed faster than the epidural group[6].

The outcome of labour was predominantly normal vaginal delivery in both groups with few instances of instrumental delivery and caesarean section and the analysis showed that these were not having any statistical significance with the mode of neuraxial analgesia. The Cochrane review of 2000 found that epidural analgesia didn't increase the incidence of caesarean sections, and the research by Sharma and colleagues was crucial in reaching this result. This was the biggest meta-analysis research, and the data clearly showed no rise in caesarean section rates; the trial conducted by Sharma and colleagues overwhelmed the other findings due to its large numbers. According to Lyon et al.[7] there was no association between epidural labour analgesia and an increase in caesarean sections.

In our study, the NRS scores before initiation of neuraxial analgesia were comparable in either group (6.7 in group Epidural versus 7 in group CSE; P =3.67). The pain scores were high, in accordance with McGill's pain questionnaire. The NRS scores after initiation of analgesia were low for the parturients who received CSE analgesia and this was statistically considerable (P<0.001). The number of epidural top-up boluses was also less for the patients who received CSE analgesia and this was also statistically considerable (P=0.001).This could be attributed to the rapid onset of analgesia due to intrathecal fentanyl and reliable sacral analgesia, which has also led to less need for further top-up boluses. This was in concordance with reports by Gambling[8] and Kayacan et al.[9]Gomez and colleagues found that in a study of 42 persons comparing CSE with conventional epidural placement for labour analgesia, women randomised to CSE required fewer top-up dosages for rescue analgesia than women randomized to the epidural. This was after analgesia was initiated with either epidural loading (8mL 0.25 percent bupivacaine) or spinal dosage (25mcg fentanyl plus 2.5mg isobaric). The latency is reduced, the duration of analgesia is prolonged, and the quality of the analgesia is enhanced when lipid-soluble opioids, like fentanyl, are added to the epidural and intrathecal regimens[10].

Maternal haemodynamics were assessed in terms of changes in heart rate as well as systolic and diastolic blood pressures at time intervals (1,5,15,30,60,90,120,180 mins). The difference between the two groups' BP and heart rate was statistically significant during these time intervals with a major drop in these parameters in patients who were given CSE analgesia. This could be attributed to the immediate and improved pain relief with catecholamines in association with combined spinal epidural analgesia. This decrease in catecholamines could in turn also lead to uterine tachysystole and foetal bradycardia. The assessment of foetal heart rate variations in either group of our study showed no instances of foetal bradycardia.

The highest sensory level obtained in patients who were given epidural analgesia was predominantly T8 followed by T10 whereas, in patients who received CSE analgesia, the level was predominantly T8 and T6. There was one parturient who experienced unilateral numbness soon after CSE analgesia. In a study by Lee BB and colleagues[11], a higher sensory block was observed in a group which received 0.25% intrathecal bupivacaine 2.5mg with 25mcg fentanyl.

None of the patients in either of the two groups had a case of maternal hypotension, bradycardia, or pruritus. Continuous CTG tracing demonstrated no evidence of foetal bradycardia.

6 LIMITATIONS

In multiparous and nulliparous women, the rate of cervical dilatation and the length of labour differed. This might be a limitation of our study. Also, the inter-individual variation in pain thresholds and drug sensitivity was another limiting factor. A neonatal assessment like APGAR was not included in our study, however, all the neonates had a reassuring status. Moreover, there have been several studies proving that low-dose epidural analgesia with opioids does not cause any adverse effects on neonates.

7 CONCLUSION

In our study comparing the two methods of labour analgesia—epidural vs CSE—we discovered that the latter had higher analgesic effectiveness. When compared, the epidural procedure slightly increased the rate of labour progression but it was within the normal limits expected for the obstetric score of the patient. The outcomes of delivery for either technique were comparable. There was no incidence of a motor blockade in either group, the sensory level attained was slightly higher for the CSE technique. The maternal hemodynamic fluctuations were typically prominent in the initial few minutes for CSE whereas it was comparable in the later hours in both the groups. We found that the maternal satisfaction scores were higher with the CSE technique.

8 FUTURE

Cynthia A. Wong et al.[12] observed Programmed Intermittent Epidural Bolus (PIEB),i.e. administration of boluses at fixed intervals in addition to Patient Controlled Analgesia (PCA) was superior to Continuous Epidural Infusions (CEI).This technique not only improves patient satisfaction but also decreases mean anaesthetic volume. Rapid drug delivery during PIEB is attributed to the better spread of the drug and action.

Dural puncture epidural (DPE) is a technical modification of the CSE in which the dura is perforated with a Whitacre spinal needle (CSE technique), but direct administration of medications into the subarachnoid space is not done. A conduit for translocation of epidural drugs from the epidural to the subarachnoid space occurs following insertion of the epidural catheter and appropriate administration of medications into the epidural space. The size of the dural puncture, the distance between the puncture location and epidural drug administration, and the pressure gradient between the two compartments determine the extent of drugs reaching the subarachnoid space.

Ultrasound imaging of the spine has recently been proposed to facilitate identification of the epidural anatomy (scoliosis) and those who are obese. Carvalho et al.[13] in their study, found a good level of success in the ultrasound-determined insertion point and very good agreement between ultrasound depth (UD) and needle depth (ND). Novel techniques to detect epidural space like epi-drum and epi-jet and epi-sure have also contributed to faster learning curve for the anaesthesiologists[14].

Protocol refinement with ultra-low-dose (<0.1%) local anaesthetic–opioid solutions with PCEA and PIEB allowing more flexibility through cost-effective smart pumps and ultrasound-guided neuraxial blocks in difficult cases can further minimize the adverse effects on progress and outcome of labour, along with improving analgesia, patient satisfaction, and reducing motor block[15]. The usage of Virtual Reality in labour analgesia is also among the latest trend which is in the pilot phase. This has greater prospects since it does not require administration of drugs and is more based on the psychological well-being of the parturient[16].

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Conflicts of interest: none

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$$\int_0^{r_2} F(r,\varphi)\, dr\, d\varphi = [\sigma r_2 / (2\mu_0)] \cdot \int_0^{\infty} \exp(-\lambda\, |z_j - z_i|)\, \lambda^{-1}\, J_1(\lambda r_2)\, J_0(\lambda r_i)\, d\lambda\,. \tag{1}$$

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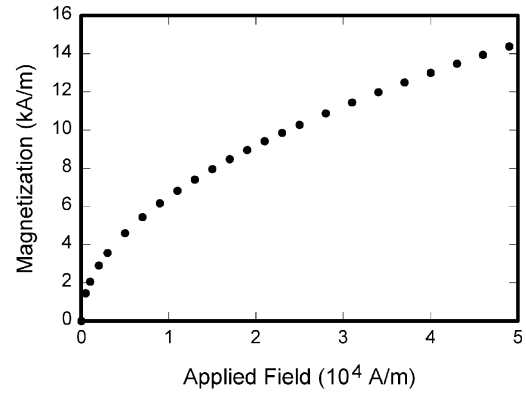

Fig. 1. Magnetization as a function of applied field. Note that "Fig." is abbreviated. There is a period after the figure number, followed by one space. It is good practice to briefly explain the significance of the figure in the caption.

Figure axis labels are often a source of confusion. Use words rather than symbols. As an example, write the quantity "Magnetization," or "Magnetization *M*," not just "*M*." Put units in parentheses. Do not label axes only with units. As in Fig. 1, for example, write "Magnetization (A/m)" or "Magnetization ($A \cdot m^{-1}$)," not just "A/m." Do not label axes with a ratio of quantities and units. For example, write "Temperature (K)," not "Temperature/K." Table 1 shows some examples of units of measure.

Multipliers can be especially confusing. Write "Magnetization (kA/m)" or "Magnetization (103 A/m)." Do not write "Magnetization (A/m) × 1,000" because the reader would not know whether the top axis label in Fig. 1 meant 16,000 A/m or 0.016 A/m. Figure labels should be legible, approximately 8 to 12 point type. When creating your graphics, especially in complex graphs and charts, please ensure that line weights are thick enough that when reproduced at print size, they will still be legible. We suggest at least 1 point.

6.3 Footnotes

Number footnotes separately in superscripts (Insert | Footnote)[1]. Place the actual footnote at the bottom of the column in which it is cited; do not put footnotes in the reference list (endnotes). Use letters for table footnotes (see Table 1). Please do not include footnotes in the abstract and avoid using a footnote in the first column of the article. This will cause it to appear of the affiliation box, making the layout look confusing.

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6.4 Lists

The IJSER style is to create displayed lists if the number of items in the list is longer than three. For example, within the text lists would appear 1) using a number, 2) followed by a close parenthesis. However, longer lists will be formatted so that:

1. Items will be set outside of the paragraphs.
2. Items will be punctuated as sentences where it is appropriate.
3. Items will be numbered, followed by a period.

6.5 Theorems and Proofs

Theorems and related structures, such as axioms corollaries, and lemmas, are formatted using a hanging indent paragraph. They begin with a title and are followed by the text, in italics.

Theorem 1. *Theorems, corollaries, lemmas, and related structures follow this format. They do not need to be numbered, but are generally numbered sequentially.*

Proofs are formatted using the same hanging indent format. However, they are not italicized.

Proof. The same format should be used for structures such as remarks, examples, and solutions (though these would not have a Q.E.D. box at the end as a proof does).

TABLE 1
UNITS FOR MAGENTIC PROPERTIES

Symbol	Quantity	Conversion from Gaussian and CGS EMU to SI [a]
Φ	magnetic flux	1 Mx $\rightarrow 10^{-8}$ Wb = 10^{-8} V·s
B	magnetic flux density, magnetic induction	1 G $\rightarrow 10^{-4}$ T = 10^{-4} Wb/m^2
H	magnetic field strength	1 Oe $\rightarrow 10^3/(4\pi)$ A/m
m	magnetic moment	1 erg/G = 1 emu $\rightarrow 10^{-3}$ A·m^2 = 10^{-3} J/T
M	magnetization	1 erg/(G·cm^3) = 1 emu/cm^3 $\rightarrow 10^3$ A/m
$4\pi M$	magnetization	1 G $\rightarrow 10^3/(4\pi)$ A/m
σ	specific magnetization	1 erg/(G·g) = 1 emu/g $\rightarrow$ 1 A·m^2/kg
j	magnetic dipole moment	1 erg/G = 1 emu $\rightarrow 4\pi \times 10^{-10}$ Wb·m
J	magnetic polarization	1 erg/(G·cm^3) = 1 emu/cm^3 $\rightarrow 4\pi \times 10^{-4}$ T
χ, κ	susceptibility	$1 \rightarrow 4\pi$
χ_ρ	mass susceptibility	1 cm^3/g $\rightarrow 4\pi \times 10^{-3}$ m^3/kg
μ	permeability	$1 \rightarrow 4\pi \times 10^{-7}$ H/m $= 4\pi \times 10^{-7}$ Wb/(A·m)
μ_r	relative permeability	$\mu \rightarrow \mu_r$
w, W	energy density	1 erg/cm^3 $\rightarrow 10^{-1}$ J/m^3
N, D	demagnetizing factor	$1 \rightarrow 1/(4\pi)$

Statements that serve as captions for the entire table do not need footnote letters.

[a]Gaussian units are the same as cgs emu for magnetostatics; Mx = maxwell, G = gauss, Oe = oersted; Wb = weber, V = volt, s = second, T = tesla, m = meter, A = ampere, J = joule, kg = kilogram, H = henry.

7 END SECTIONS

7.1 Appendices

Appendixes, if needed, appear before the acknowledgment. In the event multiple appendices are required, they will be labeled "Appendix A," "Appendix B, " etc. If an article does not meet submission length requirements, authors are strongly encouraged to make their appendices supplemental material.

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7.2 Acknowledgments

The preferred spelling of the word "acknowledgment" in American English is without an "e" after the "g." Use the singular heading even if you have many acknowledgments. Avoid expressions such as "One of us (S.B.A.) would like to thank ... ." Instead, write "F. A. Author thanks ... ." Sponsor and financial support acknowledgments are included in the acknowledgment section. For example: This work was supported in part by the US Department of Commerce under Grant BS123456 (sponsor and financial support acknowledgment goes here). Researchers that contributed information or assistance to the article should also be acknowledged in this section.

7.3 References

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7.3 Additional Formatting and Style Resources

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4 Conclusion

Although a conclusion may review the main points of the paper, do not replicate the abstract as the conclusion. A conclusion might elaborate on the importance of the work or suggest applications and extensions. Authors are strongly encouraged not to call out multiple figures or tables in the conclusion—these should be referenced in the body of the paper.

Acknowledgment

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