

Degree of pain in intravenous injection of propofol with intravenous lidocaine administration; A Literature Review Study

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Abstrak

Injeksi propofol intravena banyak digunakan untuk induksi anestesi dan sedasi, meskipun sering menyebabkan ketidaknyamanan dan nyeri di tempat suntikan, yang menyebabkan kecemasan pasien. Lidocaine, anestesi lokal, telah dipelajari kemampuannya untuk mengurangi rasa sakit ini dengan menghambat saluran natrium, sehingga mengurangi rangsangan neuron dan transmisi nyeri. Penelitian menunjukkan bahwa lidokain intravena secara efektif mengurangi terjadinya dan intensitas nyeri selama injeksi propofol. Penelitian ini bertujuan untuk menilai efektivitas lidokain intravena dalam meminimalisir nyeri yang berhubungan dengan injeksi propofol. Tinjauan pustaka dilakukan, menganalisis studi dari tahun 2018 hingga 2024 yang diperoleh dari database seperti Google Scholar, PubMed, dan ScienceDirect. Dua belas artikel yang memenuhi kriteria seleksi ditinjau. Temuan ini secara konsisten menunjukkan bahwa lidokain intravena secara signifikan menurunkan rasa sakit yang terkait dengan injeksi propofol. Selain itu, penggunaan lidokain mengurangi dosis propofol yang diperlukan dan meningkatkan kepuasan pasien. Studi menunjukkan bahwa pemberian lidokain intravena sebelum atau selama injeksi propofol adalah pendekatan praktis untuk mengurangi nyeri injeksi. Penelitian di masa depan harus fokus pada pengoptimalan parameter yang meningkatkan efek analgesik lidokain, yang pada akhirnya meningkatkan kenyamanan dan kepuasan pasien dalam prosedur yang melibatkan sedasi.

Kata kunci: Injeksi propofol, nyeri injeksi, lidokain intravena, anestesi, analgesik.

Abstract

Intravenous propofol injection is widely used for anesthesia induction and sedation, though it often causes discomfort and pain at the injection site, leading to patient anxiety. Lidocaine, a local anesthetic, has been studied for its ability to reduce this pain by inhibiting sodium channels, thereby decreasing neuronal excitability and pain transmission. Research indicates that intravenous lidocaine effectively reduces the occurrence and intensity of pain during propofol injection. This study aims to assess the effectiveness of intravenous lidocaine in minimizing pain related to propofol injection. A literature review was conducted, analyzing studies from 2018 to 2024 obtained from databases such as Google Scholar, PubMed, and ScienceDirect. Twelve articles meeting the selection criteria were reviewed. The findings consistently show that intravenous lidocaine significantly lowers the pain associated with propofol injection. Additionally, lidocaine use reduced the required propofol dosage and improved patient satisfaction. The studies suggest that administering intravenous lidocaine before or during propofol injection is a practical approach to reducing injection pain. Future research should focus on optimizing the parameters that enhance lidocaine's analgesic effects, ultimately improving patient comfort and satisfaction in procedures involving sedation.

Keywords: Propofol injection, injection pain, intravenous lidocaine, anesthesia, analgesic

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INTRODUCTION

Intravenous propofol injection is a commonly used method as an anesthetic agent for induction and sedation due to its rapid onset and short duration. However, one of the significant side effects of administering propofol is the discomfort and pain experienced at the injection site, which can cause anxiety in patients and hinder the desire to undergo

further procedures. Various studies have reported that pain during injections can be caused by several factors, including the formulation of the drug, the speed of administration, and the condition of the veins used (Ghimire & Chand, 2021),(Bakhtiari et al., 2021)

Lidocaine, which is a local anesthetic, has been researched as a preredemption to relieve pain associated with propofol injections. The mechanism by which lidocaine exerts an analgesic effect involves the blockade of sodium channels, which reduces neuronal excitability and, consequently, the transmission of pain(Wasinwong et al., 2022). Research shows that administration of lidocaine prior to propofol injection significantly reduces the incidence and intensity of pain associated with injection.

Several studies have shown the effectiveness of intravenous lidocaine in reducing pain during propofol administration. Several randomized controlled trials showed a marked reduction in pain scores among patients receiving lidocaine compared to those receiving propofol alone(Euasobhon et al., 2016). In addition, the timing and dosage of lidocaine administration have been explored, with findings suggesting that both preemptive and co-administration of lidocaine administration can be effective in reducing discomfort.

While these findings are promising, variations in methodologies and patient populations across studies indicate the need for a comprehensive review of the literature to determine optimal practices in the concomitant use of lidocaine in conjunction with propofol. Factors such as the patient's age, comorbidities, and previous experience with anesthesia can also affect the level of pain perceived, indicating the need for a tailored approach in pain management (Euasobhon et al., 2016).

In conclusion, intravenous lidocaine administration before or concurrently with propofol is a viable strategy for reducing injection-related pain. Further research into the specific parameters that maximize its analgesic effects will contribute to improved patient comfort and satisfaction during procedures that require sedation with propofol. This literature review aimed to synthesize the current evidence regarding the degree of pain associated with intravenous propofol injection and the effectiveness of intravenous lidocaine as a mitigating intervention.

RESEARCH METHOD

The method used in this study is a literature review, which is carried out to collect and analyze data related to the degree of pain in intravenous propofol injection with intravenous lidocaine administration. This process begins with searching for articles using academic search engines such as Google Scholar, PubMed, and ScienceDirect. Keywords used in the search include "Propofol injection pain," "Intravenous lidocaine," "Lidocaine for pain reduction," "Pain on intravenous propofol administration," and "Analgesic effect of lidocaine."

Furthermore, articles that are eligible for inclusion in this review must meet several selection criteria, such as publication in the period of 2018 to 2024 to ensure the relevance and up-to-date of information. In addition, the article discussed must examine the effect of lidocaine on pain due to propofol injection, both in the context of clinical studies, randomized trials, and meta-analysis, and written in English or Indonesian.

The screening process is carried out by analyzing the abstract of the articles found, where only relevant and quality articles will be included in this review. From the initial search, as many as 12 selected articles that met the eligibility criteria were analyzed in depth. This analysis includes research methods, results, and conclusions drawn from each article to identify research patterns, findings, and contributions to the topic being studied.

Data from the selected articles will be summarized and synthesized to present comprehensive information on the effectiveness of lidocaine in reducing pain due to propofol injections. These findings will be organized in relevant themes, which are

expected to provide a clear and in-depth picture of the effectiveness of lidocaine, as well as contribute to the development of clinical practice in the field of anesthesia.

RESULT AND DISCUSSION

Table 1 presents a summary of studies related to the effectiveness of lidocaine in reducing propofol injection pain in patients undergoing various medical procedures. The study included a variety of methodologies, including randomized controlled trials, that showed significant results in pain management and reduction in the need for propofol doses. This table aims to provide a comprehensive overview of the role of lidocaine in the practice of anesthesiology. The full results are presented as follows:

Table 1. Study Related to Propofol Injection Pain and Lidocaine Use

No.	Heading	Writer	Year	Methodology	Key Results
1	Comparison between Nalbuphine Intravenosa and Lidocaine in Reducing Propofol Injection Pain During Gastroscopy: A Randomized Controlled Trial	Wang et al.(Wang et al., 2020)	2020	A double-blind randomized controlled trial with 330 patients divided into three groups: nalbuphine, lidocaine, and control.	Nalbuphine and lidocaine significantly reduced propofol injection pain compared to the control group. Patients in the control group experienced higher levels of pain and needed more propofol.
2	Lidocaine in Pain Prevention in Propofol Anesthesia Induction: A Randomized Double-Controlled Clinical Trial	Buffon et al.(Luiza et al., 2020)	2020	A double-controlled randomized clinical trial on 970 adult subjects who received propofol for induction of anesthesia.	Lidocaine reduces propofol injection pain (5% vs 14.2% in saline), but the NNT (10.9) is quite high, so its use needs to be considered.
3	Intravenous Lidocaine Significantly Reduces the Propofol Dose in Elderly Patients Undergoing Gastroscopy	Hu et al.(Hu et al., 2022)	2022	A prospective, single-center, double-blind randomized controlled clinical trial in patients aged ≥ 65 years with ASA I-II. The patients were divided into two groups: the lidocaine group (n=70) and the	Lidocaine IV reduced total dose and maintenance of propofol (p<0.001), as well as reduced the incidence of intraoperative hypoxia (p=0.035), emergency airway management

No.	Heading	Writer	Year	Methodology	Key Results
				saline group (n=70).	(p<0.005), duration of gastroscopy (p<0.05), time to re-consciousness (p0.001), and postoperative pain (p=0.009). Patient satisfaction (p=0.025) and gastroscopic (p=0.031) were higher in the lidocaine group. Hemodynamic parameters, respiration rate, sedation-related events, and anesthesiologist satisfaction showed no difference between the two groups.
4	Effect of Intraoperative Lidocaine Infusion on Postoperative Pain and Quality of Recovery in Patients Undergoing Gynaecological Laparoscopic Surgery	Awal et al.(Awal et al., 2022)	2022	A randomized controlled study involving 50 female patients aged 18–55 years who underwent gynecological laparoscopic surgery, was divided into two groups (lidocaine vs. saline).	The group that received lidocaine showed significantly higher quality of recovery (QoR-40 score), faster recovery time, and a reduction in pain, nausea, and analgesic use.
5	Effect of Ondansetron Compared to Lidocaine and Placebo in Reducing Pain of Propofol Injection: A Randomized Clinical Trial	Zaazouee et al.(Zaazouee et al., 2023)	2022	A meta-analysis of 23 RCTs involving 2957 participants, with searches through PubMed, Embase, Cochrane Library, Web of Science, and Scopus up to May 2022.	Ondansetron increased postoperative discomfort rates compared to placebo (RR = 2.36) and reduced moderate (RR = 0.39) and severe (RR = 0.34) pain. However,

No.	Heading	Writer	Year	Methodology	Key Results
					lidocaine is more effective than ondansetron.
6	Comparison of Ondansetron and Lidocaine in Reducing Propofol Injection Pain: A Randomized Controlled Study	Wirat Wasinwong et al.(Wasinwong et al., 2022)	2022	The study involved 240 patients with ASA I-III classification, aged 18-65 years, undergoing elective surgery. Patients were divided into three groups: O (ondansetron 8 mg), L (lidocaine 40 mg), and C (placebo).	Group L (lidocaine) showed the lowest incidence of pain (66.2%) compared to groups O (82.5%) and C (85.0%) (P < 0.01). The median pain scores of groups L, O, and C were 2, 4, and 4.5 (P < 0.01).
7	Intravenous Lidocaine Reduces Propofol Injection Pain through Local Anesthetic and Central Analgesic Effects	Jibin Xing et al.(Xing et al., 2018)	2018	The randomized controlled study involved 1095 patients divided into groups	A dose of 40 mg of lidocaine is effective in reducing the pain of propofol injection. Lidocaine reduces pain through local anesthetic effects and central analgesic effects when the dose reaches 1.5 mg/kg.
8	Lidocaine for the prevention of pain caused by propofol injections: A controlled, randomized, and double-blind study	Sedat Kaya et al.(Kaya et al., 2022)	2022	Randomized controlled study, involving 100 women aged 18-45 years, divided into 5 groups	The use of lidocaine 20 mg with or without venous occlusion significantly reduced the incidence and intensity of pain during propofol injection compared to the control group. Vein occlusion for 60 seconds is most effective.
9	Efficacy and safety of additional	Faisal Kamal et al.(Kamal et al., 2021)	2021	A systematic review and meta-analysis of 5	Lidocaine significantly reduced the

No.	Heading	Writer	Year	Methodology	Key Results
	intravenous lidocaine for sedation in gastrointestinal endoscopic procedures: a systematic review and meta-analysis of randomized controlled trials			randomised controlled trials with 318 patients, comparing lidocaine and propofol with propofol alone.	required dose of propofol (SMD, -0.76; 95% CI, -1.09 to -0.42). There was no significant difference in the timing of the procedure or adverse events between the two groups.
10	Intravenous Lidocaine Infusion for Initial Postoperative Pain Management: A Comprehensive Review of the Controlled Trial	Robert Chu et al.(Chu et al., 2020)	2020	A review of randomized controlled trials to summarize the pharmacokinetic, antinociceptive, anti-hyperalgesic, anti-inflammatory, and side effects of lidocaine.	Intravenous infusion lidocaine is safe and effective in managing initial postoperative pain, with a loading dose of 1–2 mg/kg and a continuous infusion of 1–2 mg/kg/hour. Common side effects include hypotension, headache, and nausea. Serious effects include heart block and arrhythmias.
11	Lidocaine for reducing propofol-induced pain in induction of anesthesia in adults	Pramote Euasobhon et al.(Euasobhon et al., 2016)	2016	A systematic review of randomised controlled trials (RCTs) comparing lidocaine with placebo in reducing pain with propofol injection. It includes searching for data from various databases and meta-analysis using the Mantel-Haenszel method.	Lidocaine is effective in reducing pain after propofol injection; with a pain rate of 64% in the control group and 30.2% in the lidocaine group. Lidocaine admixture and pretreatment showed a significant reduction in pain with odds ratios (OR) of 0.19 and 0.13,

No.	Heading	Writer	Year	Methodology	Key Results
					respectively. Side effects are rare.
12	Can intravenous lidocaine definitively reduce the need for propofol and improve outcomes in colonoscopy patients using intravenous sedation?	Nongnuang et al.(Nongnuang et al., 2022)	2022	A randomized, double-blinded controlled trial on 68 colonoscopy patients, with Bispectral Index (BIS) monitoring.	Intravenous lidocaine significantly reduced total propofol use (151.76 mg vs 242.06 mg, P <.001) and improved patient satisfaction as well as the duration of BIS recovery > 85 without side effects.

Table 1 shows the results of studies on the use of lidocaine to reduce propofol injection pain, which is widely seen as an effective intervention in anesthesiology practice. Most studies confirm that lidocaine, whether administered intravenously or via infusion, is significant in reducing pain levels when injecting propofol, with studies noting a significant reduction in pain compared to the control group, highlighting the effectiveness of lidocaine in this context (Wang et al., 2020)(Hu et al., 2022).

Further, several studies compared lidocaine with other drugs, such as ondansetron and nalbuphine, and found that lidocaine was superior in terms of pain reduction (Wasinwong et al., 2022)(Zaazouee et al., 2023). This provides support for the use of lidocaine as the primary option in pain management of propofol injections. In addition, the importance of proper dosage to achieve the desired results without adverse side effects was also emphasized in the study (Kamal et al., 2021)(Chu et al., 2020), which suggests that the use of lidocaine may reduce the total dose of propofol required.

The studies also show that lidocaine is not only effective in reducing injection pain but also contributes to faster postoperative recovery, as reported in the context of gynecological laparoscopic surgery (Awal et al., 2022). Thus, the use of lidocaine in anesthesiology practice provides a dual benefit: it reduces pain during propofol injections and improves the overall patient experience.

Discussion

The use of intravenous lidocaine as a pain-relieving agent during propofol injection is an increasingly accepted approach in the practice of anesthesia. Lidocaine, known as a local anesthetic, has a mechanism of action focused on inhibiting sodium channels, which serves to block the transmission of pain signals by preventing depolarization of neuronal membranes(Herminghaus et al., 2021)(Yang et al., 2020). Thus, the use of lidocaine before or during propofol injections can reduce the pain arising from the procedure.

In the context of propofol, lidocaine not only serves to reduce discomfort, but it can also reduce the dose of propofol required to achieve the desired level of sedation. Research shows that by using lidocaine, patients are likely to require lower doses of propofol, which means reduced risks associated with propofol use, such as respiratory depression and decreased consciousness(Forster et al., 2018)(Jalota et al., 2021). This is especially important because propofol has a side effect profile that can be dangerous if not closely monitored.

Furthermore, the use of lidocaine in anesthesia practices can also contribute to faster patient recovery. Some studies show that patients who receive lidocaine experience lower pain levels and have shorter recovery times, as well as experience fewer postoperative complications (Lee & Schraag, 2022) (Joppich, 2022). This decrease in pain is directly related to increased patient satisfaction with their anesthesia experience.

Based on these evidences, it can be concluded that intravenous lidocaine offers significant benefits in managing pain during propofol injection, while improving anesthesia efficiency and overall patient satisfaction. Therefore, further research is needed to determine the optimal dosage protocol and explore the clinical applications of lidocaine beyond the use of propofol injection.

CONCLUSION

Lidocaine has been shown to be effective in reducing propofol injection pain in patients undergoing medical procedures. The use of lidocaine, either intravenously or intravenously, can significantly lower pain levels and reduce the total dose of propofol required. Therefore, lidocaine should be considered as the primary choice in pain management of propofol injections, with attention paid to the right dosage to minimize side effects. Further research is needed to determine the optimal and safe dosage and method of application of lidocaine.

REFERENCES

- Awal, S., Bhalotra, A. R., & Sharma, S. (2022). Effect of intravenous dexmedetomidine administered as bolus or as bolus-plus-infusion on subarachnoid anesthesia with hyperbaric bupivacaine. *Journal of Anaesthesiology Clinical Pharmacology*, 34(3), 46–50. <https://doi.org/10.4103/joacp.JOACP>
- Bakhtiari, E., Mousavi, S. H., & Gharavi Fard, M. (2021). Pharmacological control of pain during propofol injection: a systematic review and meta-analysis. In *Expert Review of Clinical Pharmacology* (Vol. 14, Issue 7, pp. 889–899). <https://doi.org/10.1080/17512433.2021.1919084>
- Chu, R., Umukoro, N., Greer, T., Roberts, J., Adekoya, P., Odonkor, C. A., Hagedorn, J. M., Olatoye, D., Urits, I., Orhurhu, M. S., Umukoro, P., Viswanath, O., Hasoon, J., Kaye, A. D., & Orhurhu, V. (2020). Intravenous Lidocaine Infusion for the Management of Early Postoperative Pain: A Comprehensive Review of Controlled Trials. *Psychopharmacology Bulletin*, 50(4), 216–259.
- Euasobhon, P., Dej-arkom, S., Siriussawakul, A., Muangman, S., Sriraj, W., Pattanittum, P., & Lumbiganon, P. (2016). Lidocaine for reducing propofol-induced pain on induction of anaesthesia in adults. In *Cochrane Database of Systematic Reviews* (Vol. 2016, Issue 2). <https://doi.org/10.1002/14651858.CD007874.pub2>
- Forster, C., Vanhauzenhuyse, A., Gast, P., Louis, E., Hick, G., Brichant, J. F., & Joris, J. (2018). Intravenous infusion of lidocaine significantly reduces propofol dose for colonoscopy: a randomised placebo-controlled study. In *British Journal of Anaesthesia* (Vol. 121, Issue 5, pp. 1059–1064). <https://doi.org/10.1016/j.bja.2018.06.019>
- Ghimire, B., & Chand, M. B. (2021). Lidocaine for reduction of pain induced by propofol in a tertiary care hospital: A descriptive cross-sectional study. *Journal of the Nepal Medical Association*, 59(236), 365–368. <https://doi.org/10.31729/JNMA.5796>
- Herminghaus, A., Wachowiak, M., Wilhelm, W., Gottschalk, A., & Eggert, K. (2021). Intravenous administration of lidocaine for perioperative analgesia. In *Der*

Anaesthetist (Vol. 60, Issue 2, pp. 152–160).

- Hu, S., Wang, M., Li, S., Zhou, W., Zhang, Y., Shi, H., Ye, P., Sun, J., Liu, F., Zhang, W., Zheng, L., Hou, Q., Wang, Y., Sun, W., Chen, Y., Lu, Z., Ji, Z., Liao, L., Lv, X., ... Yang, H. (2022). Intravenous Lidocaine Significantly Reduces the Propofol Dose in Elderly Patients Undergoing Gastroscopy: A Randomized Controlled Trial. *Drug Design, Development and Therapy*, 16(August), 2695–2705. <https://doi.org/10.2147/DDDT.S377237>
- Jalota, L., Kalira, V., George, E., Shi, Y. Y., Hornuss, C., Radke, O., Pace, N. L., & Apfel, C. C. (2021). Prevention of pain on injection of propofol: Systematic review and meta-analysis. *BMJ*, 342(7799), 694. <https://doi.org/10.1136/bmj.d1110>
- Joppich, R. (2022). Thema: Impact of Intravenous Lidocaine Infusion on Postoperative Analgesia and Recovery from Surgery - A Systemic Review of Randomized Controlled Trials. In *Perioperative Medizin* (Vol. 2, Issue 4, pp. 209–210). <https://doi.org/10.1016/j.periop.2010.08.004>
- Kamal, F., Khan, M. A., Lee-Smith, W., Sharma, S., Imam, Z., Jowhar, D., Henry, C., Khan, Z., Petryna, E., Patel, J. R., Qualkenbush, E. A. V., & Howden, C. W. (2021). Efficacy and safety of supplemental intravenous lidocaine for sedation in gastrointestinal endoscopic procedures: systematic review and meta-analysis of randomized controlled trials. In *Gastrointestinal Endoscopy* (Vol. 93, Issue 6, pp. 1241-1249.e6). <https://doi.org/10.1016/j.gie.2021.01.008>
- Kaya, S., Turhanoglu, S., Karaman, H., Özgün, S., & Basak, N. (2022). Lidocaine for prevention of propofol injection-induced pain: A prospective, randomized, double-blind, controlled study of the effect of duration of venous occlusion with a tourniquet in adults. In *Current Therapeutic Research - Clinical and Experimental* (Vol. 69, Issue 1, pp. 29–35). <https://doi.org/10.1016/j.curtheres.2008.02.005>
- Lee, I. W. S., & Schraag, S. (2022). The Use of Intravenous Lidocaine in Perioperative Medicine: Anaesthetic, Analgesic and Immune-Modulatory Aspects. In *Journal of Clinical Medicine* (Vol. 11, Issue 12). <https://doi.org/10.3390/jcm11123543>
- Luiza, B., Alexandre C, B., Paulo, F., Nazare O, N., Jefferson, T., & Anna Paula, P. (2020). Lidocaine in prevention of pain on propofol anesthetic induction: A randomized double-blinded clinical trial to estimate the magnitude of the effect. *Open Journal of Pain Medicine*, 4, 034–037. <https://doi.org/10.17352/ojpm.000021>
- Nongnuang, K., Limprasert, N., & Munjupong, S. (2022). Can intravenous lidocaine definitely attenuate propofol requirement and improve outcomes among colonoscopic patients under intravenous sedation?: A double-blinded, randomized controlled trial. *Medicine (United States)*, 101(39), E30670. <https://doi.org/10.1097/MD.00000000000030670>
- Wang, J., Duan, J., Xie, C., Yu, Y., & Lu, Y. (2020). Comparison Between Intravenous Nalbuphine and Lidocaine in Reducing Propofol-Induced Injection Pain During Gastroscopy: A Randomized Controlled Trial. *Pain and Therapy*, 9(2), 563–571. <https://doi.org/10.1007/s40122-020-00188-y>
- Wasinwong, W., Termthong, S., Plansangkate, P., Tanasansuttiporn, J., Kosem, R., & Chaofan, S. (2022). A comparison of ondansetron and lidocaine in reducing injection pain of propofol: a randomized controlled study. *BMC Anesthesiology*, 22(1), 1–7. <https://doi.org/10.1186/s12871-022-01650-4>
- Xing, J., Liang, L., Zhou, S., Luo, C., Cai, J., & Hei, Z. (2018). Intravenous lidocaine alleviates the pain of propofol injection by local anesthetic and central analgesic effects. *Pain Medicine (United States)*, 19(3), 598–607. <https://doi.org/10.1093/pm/pnx070>
- Yang, X., Wei, X., Mu, Y., Li, Q., & Liu, J. (2020). A review of the mechanism of the central analgesic effect of lidocaine. In *Medicine (United States)* (Vol. 99, Issue 17, p. E19898). <https://doi.org/10.1097/MD.00000000000019898>
- Zaazouee, M. S., Mahmoud, A. M., Elfar, W. H., Hana, K., Shamshoon, K. F., Adly, M.

H., Hussein, T. A., Hamza, M. M., Aly, A. A., Eguzo, M. A., Farhat, A. M., Elsnhory, A. B., Morsy, M. H., Ammar, M. F., Alnaji, A. A., Elshanbary, A. A., Shah, J., & Abdelqadir, Y. H. (2023). Effect of ondansetron compared to lidocaine and placebo for reducing propofol injection pain: A systematic review and meta-analysis of randomized controlled trials. *Medicine (United States)*, 102(38), E35021. <https://doi.org/10.1097/MD.00000000000035021>



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